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BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 20 1954

THE DIAGNOSIS OF THYROTOXICOSIS*

BY

E. J. WAYNE, M.D., Ph.D., F.R.C.P.

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Parry first described an association between thyroid enlargement and cardiac disease in 1825, and in 1835 Graves published his account of three cases of "violent and long-continued palpitations in females in each of which the same peculiarity presented itself, viz., enlargement of the thyroid gland." Each cited a case in which exophthalmos was present. It is, however, to Basedow, in 1840, that we owe the first complete clinical description of the disease which, in Europe, still bears his name. All the symptoms except tremor and most of the physical signs were described so vividly and accurately that little of importance has been added since. By comparison Sattler's book, published in 1908, though invaluable in providing information about the progress of the disease before any effective treatment was available, gives a picture which is out of perspective.

Perhaps I should apologize for retreading in this lecture much well-trodden ground. I hope, however, to deal in particular with the problem of diagnosis in the doubtful case and to discuss the value of modern laboratory tests, especially those which make use of radioactive iodine. I shall also consider some of the manifestations of thyrotoxicosis in more detail, especially where recent work has shed light on their mechanism.

Thyrotoxicosis is a relatively common disorder. It occurs in all parts of the world, but is especially frequent where endemic goitre is prevalent. Derbyshire has for long been recognized as such a district, and many of our cases have come from this region. It was this local concentration of patients that aroused my interest and provided the clinical opportunities for these studies.

The importance of suspecting the presence of thyrotoxicosis and of carrying out full clinical and laboratory investigations to establish the diagnosis cannot be overemphasized. The advance in therapeutic measures to deal with this disease has been exceedingly rapid. It is now ten years since Astwood (1943) first treated thyrotoxicosis successfully with thiourea, and the drugs in this series have given us a powerful tool with which we can almost always confirm or refute the diagnosis without subjecting the patient to forms of therapy which permanently destroy a large portion of the gland. Once the diagnosis has been firmly established other forms of treatment are available and we can offer our patients an excellent prospect of permanent recovery. Improved surgical and anaesthetic techniques have greatly reduced the risks of operation, and no patient is too ill to drink a therapeutic dose of radio-iodine. These rich opportunities in the therapeutic field impose a duty on the physician not to overlook any case in which thyrotoxicosis may be present.

In a florid case the diagnosis is obvious and can be made by the junior clinical clerk who has spent only a few weeks in the ward. On the other hand, some cases of thyrotoxicosis do not present all the classical features of the disease, and in them the diagnosis may be overlooked. This especially happens when the more prominent facial signs are lacking and there is no gross enlargement of the thyroid gland. In such circumstances the diagnosis may be difficult, for it is common knowledge that many of the clinical features associated with thyrotoxicosis may occur in a wide variety of disorders. I refer to such non-specific features as, for example, loss of weight, "nervousness," and tachycardia. Furthermore, the more definite manifestations which are often clearly associated with thyrotoxicosis may occasionally be seen in persons with normal thyroid function. Signs such as goitre, exophthalmos, and lid lag fall into this category.

Grouping of Patients

As the suspicion of the presence of thyrotoxicosis must first be assessed by the presence of some of these signs and symptoms, their incidence and diagnostic significance have been investigated more fully. This has involved dividing the patients with suspected thyrotoxicosis into two definite categories, "toxic" and "non-toxic." Such a distinction may be difficult to make and yet is essential for the practising physician. The former group essentially comprises those who will be benefited by specific therapy for thyrotoxicosis, while in the latter it is clearly not indicated. It is also of interest and importance to inquire into the prevalence of some of the clinical features often associated with thyrotoxicosis amongst people not suspected of having any thyroid disorder. We have accordingly studied the following three groups of subjects.

Group 1.—Patients referred to the thyroid clinic and shown after full investigation to be indisputably thyrotoxic. Some of these patients had clinically obvious thyrotoxicosis, but the majority had presented diagnostic difficulties to at least one clinician. The diagnosis was based on at least two radio-iodine criteria—namely, the four-hour uptake by the gland

*The Bradshaw Lecture delivered before the Royal College of Physicians of London on November 12, 1953.

and the 48-hour protein-bound activity in the plasma. If these were inconclusive or if the patient had received previous therapy, the cases were further investigated before a final decision was made. There were 90 patients in this group.

Group 2.—Patients referred to the thyroid clinic as possible cases of hyperthyroidism but finally shown to be non-toxic—72 patients fell into this group.

Group 3.—This comprised 90 normal individuals drawn so far as possible from the same social class and with the same age and sex distribution as the thyrotoxic cases. None was receiving medical attention.

The individuals in these three groups have been asked a standard set of questions and the presence or absence of certain physical signs has been recorded. Only two clinicians carried out the investigation. Fig. 1 shows

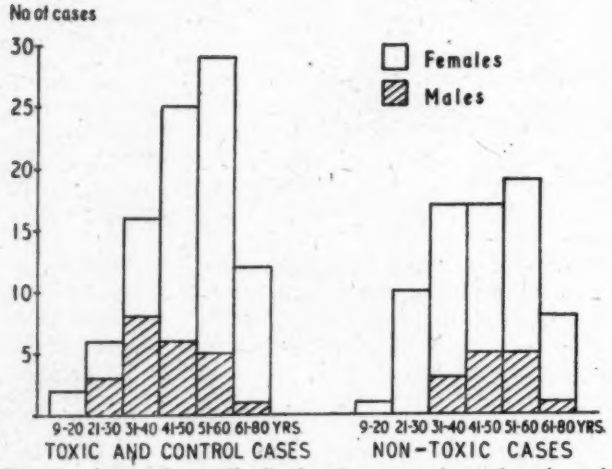

FIG. 1.—Age and sex distribution in non-toxic, and toxic and normal cases.

the age and sex distribution in the normal controls and the thyrotoxic cases and in the non-toxic group. The distribution follows the usual pattern in thyrotoxicosis. Details of the investigation will be published elsewhere (Weetch, 1954) and I shall give only a selection of the figures and a summary of our conclusions. Table I

TABLE I.—*Incidence of Signs and Symptoms in Thyrotoxic (T.), Non-toxic (N.T.), and Control (C.) Cases*

Symptoms	T.	N.T.	C.	Signs	T.	N.T.	C.
	%	%	%		%	%	%
Dyspnoea on exertion	81	61	40	Goitre ..	87	56	11
Palpitation ..	75	75	26	Diffuse enlargement	49	37	11 (slight)
Tiredness ..	80	68	31	Nodular ..	32	14	0
Preference for cold	73	53	41	Single adenoma	4	5	0
Excessive sweating	68	54	31	Exophthalmos	34	11	2
"Nervousness"	59	54	21	Lid lag ..	62	24	16
Appetite:				Hyperkinetic	39	22	9
Increased ..	32	1	2	Finger tremor	66	54	26
Diminished ..	13	14	3	Hands:			
Weight:				Sweating ..	72	54	22
Loss	52	27	2	Hot ..	76	40	44
Gain	4	7	16	Auricular fibrillation	19	8	0
Bowels:				Regular pulse rate over 90/min.	68	47	19
Diarrhoea ..	8	2	0				
Constipation ..	15	20	21				
Menses:							
Excessive ..	3	12	6				
Scanty ..	18	9	3	Average pulse rate. Beats/min.	100	85	78

shows a selection of the results of the analysis of symptoms and signs in the different groups. The signs recorded are necessarily only those which could be elicited without a full physical examination on the normal control group.

History-taking

It should be emphasized that this investigation was not made in an attempt to discover the commonest symptoms and signs in obvious cases of thyrotoxicosis, but to try to find out why there had been difficulty in separating doubtful cases into toxic and non-toxic groups on purely clinical grounds. It was decided to include a group of normal individuals when it became apparent that with some symptoms there was often remarkably little difference in the replies given by the toxic and non-toxic groups. The questions were asked in the form, "Do you become unduly breathless on exertion?"; "Do you tire easily?"; "Do you prefer hot or cold weather?"; and it is the answers to these questions which are recorded in the tables. Patients could usually give a date of onset of their symptoms, but the answers of the normal controls to the same questions varied, some having "always been like that" and others stating that "it has come on recently."

An incidental illuminating feature of this investigation was the light it threw on the art of history-taking. I can strongly recommend to any physician with a special interest in some disease, as, for example, pulmonary tuberculosis, that he put his usual questions to a group of patients with chronic anxiety or to women at the menopause. He will be surprised at the number of positive answers he receives. Yet I do not think that the experienced physician would misinterpret these replies. It is, however, this problem which confuses our clinical clerks and house-physicians, who find it far more difficult to know whether a positive answer to a question is significant. They also have less skill in framing the appropriate supplementary questions, and little experience in assessing the patient's personality as a whole. My experience in completing the forms which were used has confirmed my suspicion that methods of history-taking which involve the use of a set list of symptoms are inherently unsatisfactory.

The two surprising features of the analysis are the high incidence of many symptoms in both the non-toxic and the control groups. We believe the explanation lies in the large number of women, and especially of women at or not far past the menopause, that are present in both groups, and in the high proportion of patients with anxiety states in the non-toxic group. We have analysed separately the figures for males and females, and Figs. 2, 3, and 4 illustrate the relative frequency of three symptoms in the toxic, non-toxic, and control groups when they are broken down in this way. In the control group positive answers were given much less frequently by males. In the non-toxic group this was true of most but not of all symptoms. In thyrotoxicosis, on the other hand, the proportions of males and females with symptoms were roughly equal. This was true of all symptoms except hot flushes, which were, as would be expected, much commoner in females in all the groups. A separate analysis of the answers of women over the age of 50 showed with most symptoms a still greater difference from the males, but the numbers were too small to be able to show a statistically significant difference between women of different ages.

I shall discuss the significance of the various signs and symptoms individually, indicating those which have the greatest diagnostic value, but it may be helpful to emphasize again that the comparison is essentially between a group of thyrotoxic patients, many of whom were not severely ill, a cross-section of the community of similar age and sex distribution, and a group of patients, usually with goitre, exophthalmos, auricular fibrillation, or persistent tachycardia, many of whom had in addition the symptoms of chronic anxiety or of the menopause.

Clinical Manifestations of Thyrotoxicosis Considered Separately

I now propose to discuss the clinical aspects of thyrotoxicosis so far as they illustrate points of special diagnostic value.

Family History

There is an undoubted familial tendency to thyrotoxicosis (Rundle, 1941), but this is also true of simple goitre (Brain, 1926). The disease has been reported in identical and in dissimilar twins (Neff, 1932; Bowers, 1948; Bartels, 1953). Martin (1945) and Bartels (1953) conclude that Graves's disease is inherited in a dominant manner. Martin and Fisher (1951) could, however, find no evidence of a hereditary influence in toxic nodular goitre, but Bartels disagrees with this conclusion. Occasionally the presence of thyroid disease in a relative may direct the physician's attention towards a correct diagnosis, but usually little help is derived from the family history.

Psychological Features

In his Bradshaw Lecture last year Bomford (1953) drew attention to the importance of studying disease by psychological as well as by physical methods. Thyrotoxicosis would certainly seem to qualify as a disease with psychological aspects. Sitting in a clinic devoted to the supervision of treated cases, one can hardly fail to be impressed by the unusual temperament of those who have been cured of the somatic side of their disorder. Moreover, a previously thyrotoxic patient who has developed hypothyroidism tolerates the condition far less well than one who has developed the disease spontaneously and becomes irritated with a body which refuses to carry out efficiently the dictates of a still relatively active mind. A psychosomatic theory of thyrotoxicosis has been developed by Ham *et al.* (1951). They find that the condition tends to occur in individuals frustrated in early life who make continued efforts towards premature self-sufficiency, and when these fail develop chronic anxiety. However sympathetic one may be to the psychosomatic approach one cannot help feeling that its exponents would strengthen their case if they could foretell, even occasionally, which of the many patients with early frustration and anxiety will develop thyrotoxicosis and which are more likely to develop some other psychosomatic manifestation such as peptic ulcer, colitis, or asthma. In the few people I have known personally before they developed thyrotoxicosis I certainly would have ventured no prophecy.

A history of mental shock or emotional strain is relatively common in this disease, although patients who develop anxiety states may have been subjected to equally severe stress. It is said that the disease tends to occur at the landmarks in a woman's sexual life—puberty, engagement, marriage, pregnancy, and the menopause—but few women are far removed from one of these events. Some acute cases are clearly associated with psychical trauma or pregnancy, but in many the history of a direct emotional stimulus is absent.

It is clear that though the psychological features may be of considerable importance in the management of a case of thyrotoxicosis they are of little or no assistance in the establishment of a diagnosis.

Goitre

The high proportion of our cases in the non-toxic group who are recorded as having a goitre indicates that this is the commonest sign which gives rise to the suspicion of thyrotoxicosis. It must, however, be remembered that Sheffield lies at the tip of an area in which goitre is known to be common (Campbell, 1927), and this presenting feature may not be so common in other parts of the country. A bruit over the gland is frequently heard in severely thyrotoxic individuals but is often absent in milder cases and in toxic nodular goitres. The 11 patients in the control group recorded as having diffuse enlargement of the thyroid gland were all women, and though the abnormality was slight it might have been regarded as significant if they had presented other features of toxicity.

The problem of the distinction between thyrotoxicosis with diffuse glandular enlargement, with multiple nodules, or with a single adenoma is a difficult one. Cope *et al.* (1947) have produced evidence that some single adenomata may take up most of a tracer dose of radio-iodine while the remainder of the gland takes up very little. It is suggested that such tumours are analogous to the physiologically overactive adenomata of the islets of Langerhans or of the parathyroids, and function independently of the pituitary gland. They are rare, constituting, as in the present series, about 5% of all goitres. The common toxic multinodular goitre, on the other hand, contains nodules which have usually lowered functional activity, and the thyrotoxicosis arises from overactivity of the paranodular tissue. It is, moreover, not unusual to find adenomata in the apparently diffusely enlarged gland of Graves's disease. There is often no clear distinction, and the manifestations of thyrotoxicosis, apart from a few such as the eye signs and muscular weakness, are the result of an excess of circulating thyroid hormone and can be imitated in the normal individual by heavy dosage with thyroxine. Crile (1949), writing from a surgeon's point of view, concludes that the "fundamental issue is the age of the patient rather than the presence or absence of nodules in the thyroid." I feel sure that this is the correct approach and that the distinction between thyrotoxicosis with diffuse goitre and exophthalmos, on the one hand, and toxic nodular goitre, on the other, is worth making only when it affects the management of the case.

Eye Signs

Exophthalmos was present in about a third of our thyrotoxic cases, and, though present in 11%, was found in equal degree in only 8% of the non-toxic group, which included some cases of previously treated thyrotoxicosis. Two members of the control series showed exophthalmos of slight degree, and it should be remembered that this may be a family characteristic. We have not recorded lid retraction separately, but the distinction between lid retraction and exophthalmos, which was first pointed out by Pochin (1938), is important, since the former is much more likely to disappear after therapy (Eden and Trotter, 1942).

It has long been clear that exophthalmos is not caused simply by excess of circulating thyroid hormone, since it is absent in many cases of severe thyrotoxicosis and may be present in its most virulent form in persons with normal thyroid function. It was pointed out by Russell Brain (1945) that males are far more liable than females to develop severe exophthalmos, especially after thyroidectomy. In our series exophthalmos was twice as common in males as in females. So far as the mechanism of exophthalmos is concerned it has been suggested that the thyroid-stimulating hormone of the anterior pituitary (T.S.H.) exerts an influence not only on the thyroid gland but also on the retro-orbital tissues. Rawson *et al.* (1946) have shown that T.S.H. is normally inactivated but not destroyed by the cells of the thyroid gland and that in thyrotoxicosis the degree of inactivation is increased. Some patients, however, are thought to have thyroids less capable of effecting this oxidation, and the excess of active T.S.H. is then capable of affecting the retro-orbital tissues. No simple explanation can cover all the cases nor explain in particular why patients with intact pituitary function developing myxoedema do not exhibit exophthalmos. The possibility that two separate hormones are involved has been greatly strengthened by the recent observations of Dobyns and Steelman (1953), who have been able to obtain from extracts of anterior pituitary two hormones, one of which stimulates the thyroid gland of chickens and another which produces exophthalmos in *Fundulus*, a type of minnow. If further work confirms these separate effects in mammals, much that is at present obscure will be explained.

The tendency for exophthalmos to become progressive in a case of thyrotoxicosis seems to be related to the speed with which the concentration of circulating thyroid hormone is reduced. In our cases orbitonometric observations of the degree of exophthalmos have shown that after radio-iodine treatment, which produces its effects slowly, there is less tendency for exophthalmos to increase than after methylthiouracil or thyroidectomy (Ferguson, 1951).

Lid Lag

This was present in all our toxic and non-toxic cases with exophthalmos, but was also seen in an equal number of patients without exophthalmos. We have therefore confirmed Jackson's (1949) observations that at least 10% of normal people exhibit this phenomenon. If exophthalmos and lid retraction cannot be recognized by simple inspection of the patient it is doubtful if special signs, such as lid lag or failure of convergence of the eyes on accommodation, yield any further information of value.

Nervous and Mental Symptoms

Severe cases of thyrotoxicosis almost always show emotional instability, and milder cases may have phobias and swings of emotional tone. It is probable that the biochemical disturbance unmasks a basic personality defect. It is easy to regard some patients as primarily psychotic unless the physician or psychiatrist has the possibility of thyrotoxicosis in mind.

In our series we asked the questions, "Are you a nervous person?" and "Are you irritable?" and, if the answer was positive, inquired whether this had always been so. About a quarter of the normal controls answered "yes" to both questions, and several members of the older age groups declared that the symptoms were of comparatively recent onset. Females gave a positive answer much more often than males (Fig. 2). In the non-toxic group as many females gave a positive answer as in the toxic group, but the complaints were usually long-standing except in females at or about the menopause. Neither of these symptoms therefore carried much weight diagnostically except in males. Hyperkinetic movements were significantly more frequent in toxic cases, and this sign has some diagnostic value when it is present. Finger tremor was recorded whether it was fine or relatively coarse. It is very common in apprehensive persons and in the older age groups. A fine rapid tremor was much more often seen in the thyrotoxic group, but may occur in normal people. Jackson (1949) found it in about 2% of his series. Unfortunately, this type of tremor, usually considered to be characteristic of thyrotoxicosis, tends to grade imperceptibly into the slightly coarser types seen in anxiety states, and is of little diagnostic help in separating the two groups.

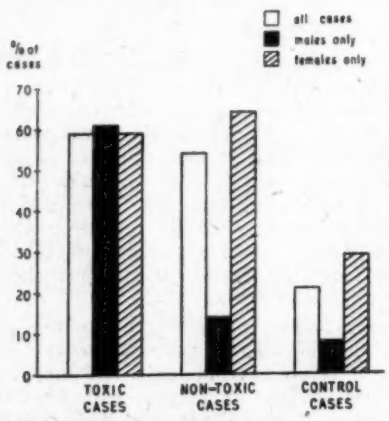

FIG. 2.—Incidence of nervousness in all cases, in males only, and in females only.

Muscular System

Muscular weakness and easy liability to fatigue are frequent accompaniments of the thyrotoxic state. The muscles may show histological changes which are probably due to excess of T.S.H. rather than of thyroxine (Dobyns, 1946). About a third of the control series said that they tired easily, and as large a proportion of the non-toxic as of the toxic patients had the symptom. Here again a positive answer to the question is of value in the male but of little help in the female unless there has been a definite alteration of recent date.

Cardiovascular Manifestations

I have recently discussed the circulatory adjustments which take place in thyrotoxicosis (Wayne, 1952), and I shall not deal with them in detail here. They are all due to excess of circulating thyroid hormone and can be reproduced in animals. It is, however, still uncertain whether there is a specific type of heart disease caused by thyrotoxicosis or whether an excess of thyroid hormone acts merely as a precipitating factor in hearts already predisposed to failure from other causes. Levine (1951) takes the former view, but the balance of evidence is in favour of the latter. A distinction between thyrotoxicosis and thyrotoxic heart disease is worth making, since auricular fibrillation or congestive failure, when it occurs in thyrotoxicosis, becomes more important than the purely metabolic effects of the hormone. This is, however, one of the few forms of heart disease which can be treated by removing the cause.

Cases of thyrotoxic heart disease may present with established auricular fibrillation or attacks of paroxysmal fibrillation. Clinical examination of the heart sometimes gives rise to the suspicion that mitral stenosis is present, since the first sound at the apex may be accentuated and so roughened as to suggest a presystolic murmur; systolic murmurs are also often heard. It is in such cases and in cases with congestive failure that tracer tests with radio-iodine may be the only method of making a diagnosis without subjecting the patient to a prolonged therapeutic trial. One feature which may suggest that auricular fibrillation is secondary to thyrotoxicosis is its not infrequent failure to respond by a fall in rate to the administration of digitalis in full doses.

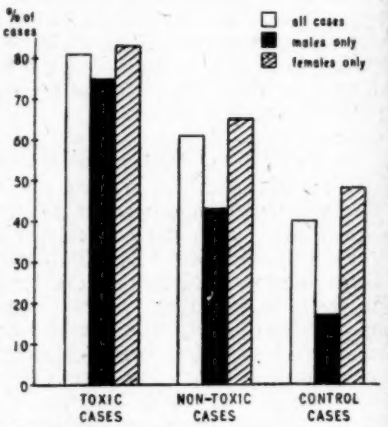

FIG. 3.—Incidence of dyspnoea on exertion in all cases, in males only, and in females only.

In our series of cases the average pulse rate in patients with regular rhythm was significantly higher than in the non-toxic and control groups, but there was considerable overlap between individual cases. We have, however, seen cases of undoubted thyrotoxicosis with resting pulse rates below 80 beats a minute. A slowing of the pulse rate during sleep occurs in normal and neurotic individuals but not in thyrotoxic patients. This is one of the most valuable differentiating features after admission to hospital. Breathlessness on exertion and palpitation occur so frequently in anxiety states and in normal women that they have little differential diagnostic value (Fig. 3).

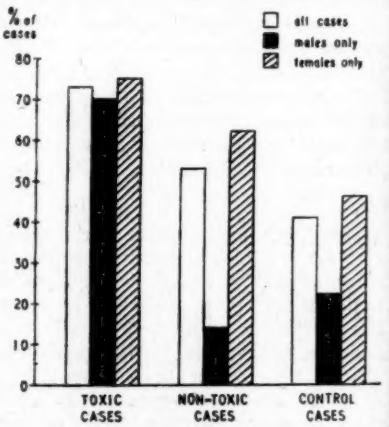

FIG. 4.—Incidence of preference for cold weather in all cases, in males only, and in females only.

The Skin

Because the metabolic rate is high and excess heat must be eliminated, the skin of the thyrotoxic patient is typically hot and moist. Patients often say that they dislike the heat, and they may complain of hot flushes. A surprisingly large proportion of our group of normal individuals expressed a preference for cold weather, but, as Fig. 4 shows, it is chiefly women who dislike a hot environment. Thyrotoxic patients in general expressed their dislike of hot weather much more

vehemently than the non-toxic and control groups and complained more convincingly of excessive sweating. These two symptoms have a diagnostic value even in the female if the questions are properly framed.

Although hot and sweating hands are a characteristic feature of the florid thyrotoxic case, they may, of course, be seen in normal persons, and the nature of the environment must be taken into account. If the atmosphere is relatively dry and cool and the hands are sweating they may be cool to the touch. It is very rare for them to be cold except occasionally in cases with severe congestive failure, although we have noted cold feet, especially in elderly patients.

Appetite and Loss of Weight

Although only a third of the patients with thyrotoxicosis said that their appetite had increased, this symptom is so uncommon in the other groups that it has special diagnostic value. Patients with anxiety state usually have diminished appetites. No fewer than 14% of toxic cases, however, said that their appetite was diminished, and these were often the severer cases. Loss of weight is also a valuable differential diagnostic feature, although 4% of toxic patients gave evidence of gain of weight. We adopted the arbitrary figure of a loss of 7 lb. (3.2 kg.) or more. Greene (1953) has recorded a loss of weight in 44% of patients and a gain in weight of 10% of patients with goitre, not all of whom, however, were toxic. Conway (1950) investigated the weights of 50 cases of active Graves's disease and found that 7 were heavier and 33 lighter than the expected weight. Appetite was increased in 38 of the cases and poor in 1. The combination of loss of weight with increased appetite when present is diagnostic of thyrotoxicosis and was not found in any of our non-toxic or control groups.

Bowel Function

Diarrhoea occurred in about 8% of the patients with thyrotoxicosis. Very rarely it may be the presenting symptom. Constipation, on the other hand, is by no means uncommon. It is of some interest that 20% of the normal controls and of the non-toxic group were constipated and most of them took purgatives regularly. This no doubt explains the preponderance of advertisements for purgatives among the medicaments offered to the public in the popular press.

Menses

Irregularity of menstruation was found in about one-fifth of the premenopausal patients in both toxic and non-toxic groups, but scanty periods were more common in the former. The numbers of patients are, however, small. Riisfeldt (1948), in a series of 340 women, found menstrual abnormalities in 31% of cases of toxic diffuse goitre, 21% of toxic nodular goitre, and 10% of patients with non-toxic goitre. Diminution in the menstrual loss was more common than increase.

The Spleen

We have been unable to confirm the belief that clinically determinable enlargement of the spleen occurs in thyrotoxicosis, although Williams (1946) found it in 10% of 247 cases. In the few instances in which it has been present in cases of thyrotoxicosis which have passed through our hands there has always been some other cause, such as chronic microcytic anaemia.

General Conclusions

We had hoped, when we began this survey in our three series of cases, that we might be able to discover some signs or symptoms which would enable a distinction to be made between thyrotoxic and non-toxic cases on purely clinical grounds. In fact, we discovered that most of the classical signs and symptoms are a reliable guide in thyrotoxic males, but that the problem was far more difficult in females. Women, especially women at the menopause, will often say they have symptoms such as breathlessness on exertion or fatigue even if they are carrying out a full day's work. When in addition they have an anxiety state it is impossible to distinguish thyrotoxic from non-toxic cases on symptoms alone. The problem, however, becomes difficult chiefly when these symptoms are associated with some objective feature usually associated with the thyrotoxic state, such as goitre, exophthalmos, auricular fibrillation, congestive failure, or persistent tachycardia. The most helpful diagnostic features when they are present are increased appetite, loss of weight, preference for cold weather, hot and sweating hands, persistent tachycardia especially during sleep, and hyperkinesis. The value of any diagnostic feature is greatly enhanced if it is of relatively recent onset.

It is clear that in the doubtful case laboratory help is needed, and I shall now discuss the various tests which have been devised to assist the clinician.

Special Tests of Thyroid Function

Further evidence that it is not always easy to arrive at a diagnosis of thyrotoxicosis on clinical evidence alone is provided by the variety of laboratory methods which have been used to assess thyroid function. Some of these are now only of historical interest, but I shall review briefly those which are still in vogue, devoting, however, most of my time to a discussion of the help which may be afforded by tests using radio-iodine.

Estimation of the Basal Metabolic Rate.—This is still the standard laboratory investigation used by most clinicians in an attempt to confirm or refute a diagnosis of thyrotoxicosis. It has the merit that it is comparatively easy to carry out, and it gives some idea of the severity of the thyrotoxic state in clear-cut cases. It is essentially a measure of hypermetabolism, and a raised basal metabolic rate is therefore found in a variety of other conditions, as, for example, leukaemia, phaeochromocytoma, cardiovascular disease, and anxiety states. In the last two conditions it may be impossible to achieve truly basal conditions without heavy sedation (Rapport *et al.*, 1951). Thyrotoxic patients may, moreover, have basal metabolic rates lying within the statistically acceptable "normal" range. In our experience (Goodwin *et al.*, 1951) as many as 33% of patients with proved thyrotoxicosis may have basal metabolic rates lying below +20%, and Foote *et al.* (1952), who took special care to obtain reliable estimates, found that 23% of thyrotoxic patients had basal metabolic rates lying within the normal range. Werner and Hamilton (1951) also report 15 cases of hyperthyroidism without hypermetabolism. Robertson (1952) has pointed out that a specially careful technique and standards derived from normal persons in Great Britain should be used, and Robertson and Reid (1952) emphasized the value of carrying out further tests after the administration of iodine in doubtful cases. An estimation of the basal metabolic rate is of undoubted help in a suspected case of thyrotoxicosis, but conditions must be truly basal and observations on out-patients are often unsatisfactory. Duplicate determinations on two or more days are desirable, and in border-line cases further investigation after the administration of iodine may be necessary.

Estimation of Serum Protein-bound Iodine.—This estimation measures the amount of circulating iodine bound to protein molecules, and is generally regarded as an accurate index of the amount of circulating thyroxine. Several groups of workers in the U.S.A. (Salter *et al.*, 1941; Starr *et al.*, 1950; and Hallman *et al.*, 1951) regard a raised level as the most reliable laboratory evidence of thyrotoxicosis. De Mowbray and Tickner (1952), on the other hand, in this country found that the level was raised in only two-thirds of cases of proved hyperthyroidism, and regard the estimation as inadequate in itself as a test of thyroid function. The previous administration of iodine-containing compounds produces a spurious increase in the serum protein-bound iodine figures. We have encountered serious technical difficulties with the method of Barker *et al.* (1951). It is doubtful if this estimation, which is in any case time-consuming, will ever become generally available to the clinician. It is chiefly of interest because it may give a

more complete picture of iodine and thyroxine metabolism when the results of simultaneous studies with radio-iodine are available (Riggs, 1952).

Estimation of Serum Cholesterol.—The serum cholesterol is lower than normal in the majority of cases of thyrotoxicosis. There is an increased rate of hepatic synthesis of cholesterol, but this is accompanied by an even greater rate of destruction and intestinal excretion. The changes are not related directly to changes in metabolic rate (Rosenman *et al.*, 1952). The fall in blood cholesterol level is small in degree, but under treatment a steady rise occurs (McGavack and Drekter, 1945). We have found the estimation of serum cholesterol of little diagnostic help in thyrotoxicosis although it is valuable in suspected cases of myxoedema. Our experience thus agrees with that of Peters and Man (1950) and Bartels (1950).

Estimation of Serum Creatine.—Creatinuria undoubtedly occurs in all patients with thyrotoxicosis, but its degree bears no relation to the severity of the disease. Griffiths (1951) has suggested that a knowledge of the height of the fasting serum creatine is of diagnostic value in thyrotoxicosis, especially when considered in conjunction with the basal metabolic rate. Unfortunately, however, he appears to have accepted a level of 0.6 mg. of creatine per 100 ml. as the upper limit of normal in spite of the observation of Tierney and Peters (1943) that normal women often have a serum creatine higher than this figure. Because of the high degree of overlap which exists between thyrotoxic and normal men and women it is unlikely, even if a more sensitive method of estimating serum creatine could be devised, that the differences would be clear-cut enough to be of diagnostic value. Similar considerations apply to creatine-tolerance tests.

Blood Picture.—"Leucopenia is fairly common, and it has been claimed that relative or absolute lymphocytosis is a constant finding in hyperthyroidism" (Whitby and Britton, 1950). If this were true an examination of the blood would clearly be diagnostically helpful. My colleague Dr. E. K. Blackburn (1953, personal communication) has studied the peripheral blood in 51 of our proved cases of thyrotoxicosis. In none of these was there a leucopenia or an absolute lymphocytosis, taking the respective normal ranges as 4,000–11,000 per c.mm. and 1,000–4,500 per c.mm. (Osgood *et al.*, 1939). In his view the concept of relative lymphocytosis should be abandoned. The bone marrow has, however, shown a lymphocytic reaction in some cases. This is probably a manifestation of the general tendency to hyperplasia of lymphoid tissue in this disease. Anaemia, when it occurs, is usually of iron-deficiency type unrelated to the thyrotoxicosis, except in so far as the latter predisposes to achlorhydria.

Use of Radio-iodine in Diagnosis of Thyrotoxicosis

Pochin (1950), in his Oliver-Sharpey Lectures, described the ways in which radio-iodine may be used to investigate fundamental problems of iodine metabolism, and Myant (1952) has described and critically reviewed the different types of test which may be used to assess thyroid function. These tests fall into two main groups: they either measure directly or indirectly the capacity of the thyroid gland to take up radio-iodine, or they attempt to measure the output of radioactive thyroxine from the gland. The avidity of the thyroid for iodine, which is greatly increased in thyrotoxicosis, can be estimated by determining the proportion of a given dose taken up by the gland at a fixed time or the maximum amount taken up by the gland. Alternatively, the rate at which the dose is taken up at a given plasma concentration of radio-iodine may be measured, a figure which is termed the thyroid clearance rate by analogy with renal clearance rates. Theoretically this should be a more reliable index of thyroid activity than the total radio-iodine uptake. Since the administered radio-iodine is shared between the thyroid and the kidneys, an estimation of the amount of radioactivity in the urine will give an indirect measure of the capacity of the thyroid to absorb iodine. Samples of urine taken at various times after the test dose are usually analysed separately.

The thyroid converts the radio-iodine into radiothyroxine at a rate and to a degree which is determined by its functional activity. Twenty-four to forty-eight hours after a tracer dose has been given the plasma of normal individuals shows little or negligible radioactivity. On the other hand, the plasma of the thyrotoxic patient contains a significant amount of radioactive material, of which a high proportion is bound to protein. Tests of this type involve the examination of a blood sample at a fixed time after the administration of the test dose, and an estimation of the relative amount of radioactivity in inorganic and organic forms.

Many groups of observers have carried out investigations on normal individuals and on patients with thyrotoxicosis, using one or more of these methods. We (Goodwin *et al.*, 1951) compared seven different criteria in normal persons, in patients with definite thyrotoxicosis and in patients in an "intermediate" but non-toxic group with goitre, treated thyrotoxicosis, or anxiety state. We came to the conclusion that the index which correlated best with the final clinical diagnosis, arrived at independently of the results of radio-

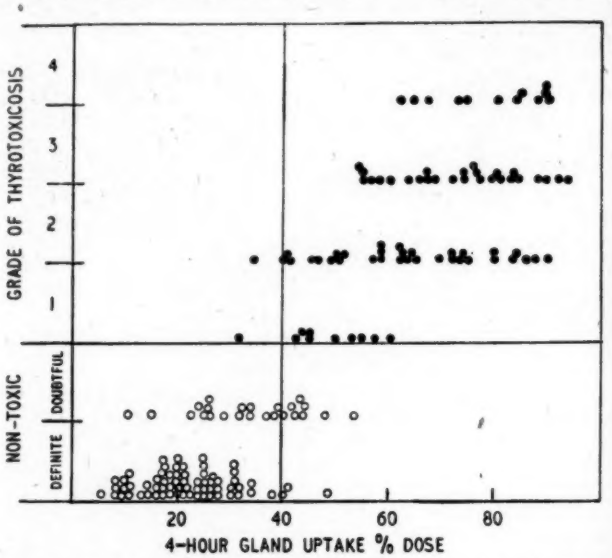

FIG. 5.—Relation of level of thyroid function to uptake of radio-iodine after four hours.

iodine tests, was the protein-bound plasma activity measured 48 hours after the administration of the dose. We thought, however, that, whenever possible, more extensive studies should be carried out. Subsequently we (Ansell *et al.*, 1953) selected three radio-iodine tests and applied them to a group of 179 persons, all of whom had been carefully and independently assessed clinically. These tests were the proportion of the dose taken up by the gland four hours after administration, the clearance rate of radio-iodine from the plasma one hour after administration, and the protein-bound plasma activity 48 hours after administration. Figs. 5 and 6 show the results which we obtained.

All thyrotoxic cases were classified into one of four grades of severity, and the non-toxic group was divided into those cases in which there was no clinical doubt that the patient had normal thyroid function and those about which there had initially been some doubt that the patient might be thyrotoxic. It is this group which any satisfactory test must separate accurately from cases of mild thyrotoxicosis. It will be seen from Fig. 5 that if a 40% uptake by the gland four hours after the radiation had been given was taken as the dividing line it separated fairly well non-toxic from thyrotoxic individuals, and that the results ran roughly parallel with the degree of severity of the disease. High uptakes did, however, occur in non-toxic individuals. If we took a clearance rate of 80 ml. a minute as the dividing line between toxic and non-toxic persons we found that several thyrotoxic patients had clearance rates well below this level. The protein-bound plasma activity, however

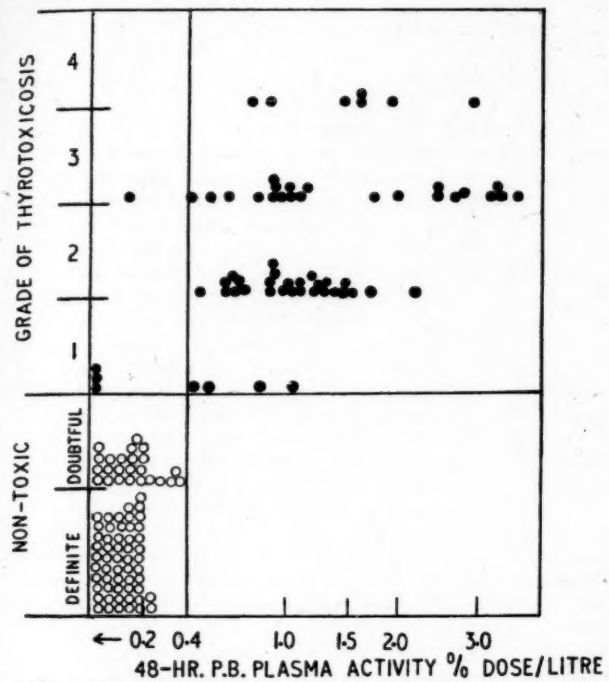

FIG. 6.—Relation of level of thyroid function to 48-hour protein-bound plasma activity. (Scale not strictly logarithmic below 0.2%.)

(Fig. 6), showed a fairly sharp division between the two groups, although thyrotoxic patients occasionally had levels well below our normal limit of 0.4% of the dose per litre. We concluded that the tests of four-hour uptake by the gland and protein-bound plasma activity at 48 hours would usually give consistent results and separate toxic from non-toxic cases.

We have now carried out more than 750 tracer tests of this type, and our conclusions, based on the smaller number of cases shown in Figs. 5 and 6, must be modified. Dr. Miller and I have correlated these figures with the clinical findings where they were available. Fig. 7 shows the results plotted so as to emphasize the cases of agreement or disagreement between the four-hour gland uptake and the 48-hour protein-bound plasma activity. Rectangles B and D contain cases in which both tests gave results which were in agreement. When this is so, it is quite exceptional to find a discrepancy between the clinical diagnosis and the radio-iodine tests, and we would place the error at less than 1%. It should be stated, however, that some cases were referred from other clinicians, and we cannot be sure that in some cases the tests have not been taken into account in arriving at a conclusion. A large proportion were, however, patients under our own care, and we can say with certainty that when the diagnosis is clear on clinical grounds the two radio-iodine criteria are always concordant and confirmatory.

We have ourselves examined the records of all the available patients in which the results of the two tests were discordant, that is to say, of cases falling in rectangles A and C. Black points appearing in rectangle A and white ones in rectangle C are examples of correct results by the plasma-activity test but incorrect as judged by the four-hour gland uptake. White points in rectangle A and black points in rectangle C indicate the converse. It will be seen that the black points fall about equally in rectangles A and C, but the white ones are mainly in rectangle C. The protein-bound plasma activity is therefore a more accurate index than the four-hour gland uptake. It is, in fact, about twice as reliable, but only because it agrees with the clinical diagnosis better in non-toxic cases. A similar analysis of the figures for the thyroid clearance rate shows that they correlate better with the clinical diagnosis than the four-hour uptake, but less well than the protein-bound plasma activity.

There are certain important circumstances in which radio-iodine tests give results which must be interpreted with reserve. These are the previous administration of iodine or iodine-containing compounds, the administration of drugs of the thiouracil series, previous treatment by thyroidectomy or radio-iodine, and in cases of myxoedema or cretinism. We have examined the records of 47 cases which gave discordant results in the two tests and in which one or other of these factors had to be taken into account. These are not plotted in Fig. 7.

The administration of inorganic iodine or iodides diminishes the amount of radio-iodine taken up by the gland, and it is wise to wait for three weeks after stopping these drugs before carrying out tracer tests (Keating *et al.*, 1950). Plasma activity is also reduced (Ansell and Miller, 1952). We therefore carry out a simple test described by Foote *et al.* (1952) for iodides in the urine. The organic iodine compounds used in diagnostic radiography also affect radio-iodine criteria, but do not yield enough iodine to give positive readings in this test. We have found that individuals with normal thyroid function may show complete suppression of radio-iodine uptake 18 months after they have been given iodized oil for bronchography. They should be specifically questioned about previous *x*-ray investigations.

Drugs of the thiouracil series administered over a period of time may cause an increased uptake of radio-iodine by the thyroid which can persist for as long as three years (Foote *et al.*, 1952). In our series plasma activity was a much more accurate index in such cases.

After thyrotoxicosis has been treated either by thyroidectomy or by radioactive iodine the 48-hour plasma activity tends to be higher than would be expected from clinical estimates of thyroid function. In general, it can be said that the uptake or clearance is a more reliable index than plasma activity in assessing the results of these two forms

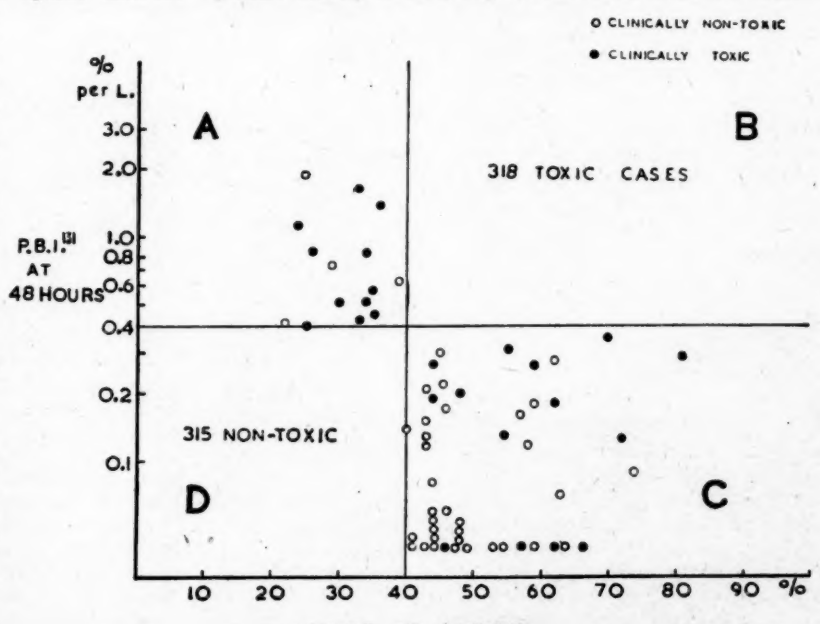

FIG. 7.—Relation of four-hour gland uptake to 48-hour protein-bound plasma activity levels.

of treatment (Ansell *et al.*, 1953). Similarly in hypothyroidism not amounting to complete myxoedema, high protein-bound plasma figures may be obtained in spite of clinical evidence of diminished thyroid function. The explanation of these exceptional results is not clear, but it seems probable that in these cases the specific activity of the circulating thyroxine is increased. The thyroid gland is working to the maximum of a diminished capacity to synthesize thyroxine and is turning over the iodine presented to it at an unusually rapid rate, so that a relatively large proportion of the circulating thyroxine molecules contain radioactive atoms. This hypothesis has been shown to be correct in two cases of hypothyroidism in which simultaneous estimations of circulating non-radioactive protein-bound iodine were carried out (Blom and Terpstra, 1953). In familial cretinism, in which hypothyroidism is associated with both a high uptake by the gland and high protein-bound radio-iodine activity, it seems more likely that there is a more fundamental disturbance in iodine or thyroxine metabolism (Hubble, 1953; McGirr and Hutchison, 1953).

We have no doubt that it is always preferable to carry out at least two and preferably three of these tests, and at Sheffield these are always done. An estimation of the 48-hour protein-bound plasma activity alone may, however, be of great diagnostic value. Since the patient need not come into contact with electronic apparatus it is possible to provide a diagnostic service for hospitals far removed from the centre at which the actual estimations are carried out. Doses of radio-iodine are dispatched weekly and a single sample of plasma is returned from each patient. Macgregor *et al.* (1953) have recently reported the results of such a co-operative effort between our centre and Nottingham. The patients were seen by two physicians, and in doubtful cases the final diagnosis was made only after therapeutic trials and follow-up.

Similar tests have been carried out at Derby and Scunthorpe, but the conditions were less rigorously controlled and the final clinical diagnosis may in some instances have been influenced by the results of the test. The correlation between the clinical and laboratory results at the three centres is summarized in Table II. It will be seen that an incorrect conclusion was given by the radio-iodine criterion in about 8% of cases, the test mainly tending to show non-toxic results in clinically toxic cases. This is especially true of borderline or doubtful cases.

TABLE II.—*Correlation Between the Final Clinical Diagnosis and the Conclusions Based on a Single Estimation of the* 48-*hour Protein-bound Plasma Activity*

	No. of Cases	Clinical Diagnosis	Correct	Incorrect
Nottingham	50	Toxic	25	2
		Non-toxic	22	1
Derby	77	Toxic	22	2
		Non-toxic	51	2
Scunthorpe	43	Toxic	13	6*
		Non-toxic	24	0
Total ..	170		157	13†

* 5 "mild" or "doubtful."
† 3 clinically non-toxic cases returned as toxic; 10 clinically toxic cases returned as non-toxic.

General Conclusions on Plasma Activity Tests

When we consider together the 1,000 tests of protein-bound plasma activity which we have carried out we arrive at the following general conclusions. The test alone has an error of about 10%, assuming the clinical diagnosis to be correct, but it must be remembered that this itself is not 100% accurate. When the results are supported by simultaneous estimations of clearance rates or uptake figures, great confidence can be placed in the results. If uptake and plasma activity figures are discordant the latter is more likely to be correct. It is unlikely to suggest that a patient is thyrotoxic without this being the case. It is better, however, in such instances to carry out a therapeutic trial. Little help is gained by repeating the tests, which almost always give the same results. Uptake clearance and plasma activity figures must be interpreted with reserve in patients who have received previous therapy.

All radio-iodine tests have certain drawbacks, and the ones which we use are not immune from criticism. It is possible by using a scintillation counter to determine the uptake of radio-iodine by the gland with as little as 5 microcuries of I^{131}, but to determine with reasonable accuracy the lower levels of plasma activity at least five times this amount must be used. Even so, the radiation hazard is less than that of some common diagnostic *x*-ray procedures, and the dose is less than a hundredth of that used in the treatment of thyrotoxicosis. Nevertheless, it is desirable to reduce to the absolute minimum the amount of radiation to which the gland is subjected. One way of achieving this result is to administer a drug of the thiouracil series an hour before the radio-iodine is given (Stanley and Astwood, 1948), or, alternatively, sodium iodide may be given together with the radio-iodine intravenously (Newsholme, 1952). Either the clearance rate (Newsholme) may be used or the maximum uptake of I^{131} by the thyroid together with a factor acting as an index of the initial slope of the curve (Foss and Herbert, 1952). These tests also have the advantage of being relatively unaffected by an increase in the iodine intake.

The avidity of the thyroid gland for iodine is most simply measured by determining the proportion of a dose excreted in the urine. The advantages of this method are its applicability to out-patient cases, the small dose of radio-iodine used, and the relative simplicity of the physical measurements. One disadvantage is the difficulty of ensuring that the whole of the urine output has been preserved for analysis, a difficulty which we have experienced with female patients even when they have been in our wards. We found that the excretion of radio-iodine in the urine during the 24 hours after it had been administered was a relatively poor index of thyroid function (Goodwin *et al.*, 1951). Fraser and his co-workers (1953) have, however, shown that by collecting the urine separately during the periods 0–8 hours, 8–24 hours, and 24–48 hours three indices of thyroid function could be derived. These were used to check for errors of collection and technique, and to correct for the presence of renal disease. The deductions made from them usually correlated well with the presence or absence of hyperthyroidism, and could be used to confirm the existence of myxoedema. The method appears to suffer, however, from the general defect of uptake measurements which we have also found since it tends to place non-toxic nodular goitres in the toxic range.

Fraser (1953) has recently shown that a method described by Berson *et al.* (1952) yields satisfactory results in both hyperthyroidism and hypothyroidism. The method has the disadvantage of requiring the intravenous administration of the radio-iodine, but the test, which is essentially a clearance test, can be completed in an hour.

Choice of a Radio-iodine Test

It will be seen, then, that all the tests which are at present available have both advantages and disadvantages. Our experience leads us to believe that it is best to determine both the iodine uptake of the gland and the protein-bound plasma activity. The latter measurement alone is simpler, and can be completed without the patient attending the diagnostic centre. The urine-excretion test as modified by Fraser is technically simple if appropriate samples can be delivered to the centre, and is of especial value in assessing hypothyroid states. Those who contemplate setting up a radio-iodine diagnostic service would be well advised to concentrate on one or two of the available tests, and to establish their own ranges of normal and abnormal values. We have some evidence that there are differences in the levels indicating abnormality in different countries and even in different parts of the same country. Most of our patients

come from an area which is known to be relatively iodine deficient (Murray *et al.*, 1948), and our criteria may not be generally applicable.

Relative Value of Different Tests of Thyroid Function

Each of the available tests measures a different aspect of thyroid function. Those using radio-iodine indicate either the capacity of the thyroid gland to concentrate iodine or its ability to turn out radioactive thyroxine, but they do not measure the absolute rate of iodine metabolism. The former test is affected by the variation in the plasma iodide level, and the latter by the thyroxine content of the thyroid. Both must be interpreted with reserve when the patient has received iodine-containing compounds or has been subjected to any therapeutic procedure. The basal metabolic rate, even after a hypnotic, measures hypermetabolism which may be due to a variety of "extra-thyroid" causes (Meckstroth *et al.*, 1952). It does, however, give some indication of the degree of severity of the condition. The estimation of the non-radioactive serum protein-bound iodine should theoretically give the most direct measurement of circulating thyroxine, but is technically difficult. But even if we knew with certainty the absolute level of circulating thyroxine we should have to take into account the general biological phenomenon of the variability of the response of different individuals to the same stimulus.

Myant (1952) has said, "However we define normality, the limit we set between normal and pathological is an arbitrary one, and no test can tell us what this limit should be." From the point of view of the biologist this is true, and with sufficiently sensitive tests we should probably find a graded response to increasing doses of thyroxine. It is even possible that some of the symptoms of those who have an anxiety state are produced by a slight excess of the thyroid hormone. On the basis of blood iodide studies Brody (1949) has produced evidence that this may be so, and Fraser *et al.* (1953) noted a tendency for his "neurosis" group to have a relatively high gland uptake of radio-iodine. The possibility is intriguing. Yet such persons do not respond to therapeutic tests which diminish the activity of the thyroid gland. Our correlations are ultimately based on this response, and it is this aspect in which the clinician is primarily interested. Our preference for radio-iodine tests is founded on the fact that by their use we are able to make a decision quickly on whether or not specific treatment shall be instituted, and they are of minimum inconvenience to the patient. We believe that they will be widely used in the future.

Conclusion

I hope I have been able to convince you that, while it may be very easy to make a diagnosis of thyrotoxicosis from the history and physical examination alone, it is often very difficult and there will always be patients about whose thyroid function the physician remains in doubt. Some symptoms and signs have greater diagnostic value than others; diagnosis is relatively easy in the male, but difficult in the female, especially if she is in a state of chronic anxiety.

When there is any question about the diagnosis, therapeutic tests should be carried out, but much time may be saved by studies of iodine metabolism, using isotope techniques.

I wish to thank my clinical colleagues at Sheffield who have referred cases to me, and Dr. D. V. Hubble, of Derby, and Dr. J. H. D. Millar, of Scunthorpe, for detailed information about cases at these centres. The work on radio-iodine was made possible through the collaboration of Mr. G. W. Blomfield, the Director, and Dr. H. Miller, the senior physicist of the Sheffield National Centre for Radiotherapy. Figs. 5 and 6 are reproduced by permission from *Radioisotope Techniques*, Proceedings of the Isotope Techniques Conference, Oxford, Volume I. H.M.S.O., 1953.

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The Wellcome Trust has set aside a further £10,000 for whole-time Research Fellowships in Schools of Pharmacy in Great Britain. The Trustees made their first grant of £5,000 for Research Fellowships in 1947. They added a further £1,200 last year, when five Fellowships were awarded, and the value of each was raised from £350 to £400 a year. The awarding committee, nominated by the Wellcome Trustees and the Pharmaceutical Society of Great Britain, has discretion to award a senior Research Fellowship at a somewhat higher rate. Fellows must be registered pharmaceutical chemists in Great Britain, or graduates in pharmacy of a University in this country. A Fellowship is tenable for two years on annual award and is renewable in exceptional circumstances for a third year.

IODOTHIOURACIL IN TREATMENT OF TOXIC GOITRE

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In 1948 Barrett, Goodman, and Dittmer synthesized several organic combinations of halogens with thiouracil, of which 5-iodo-2-thiouracil proved most suitable for clinical trial. Because of the avidity of the hyperthyroid gland for iodine, the concentration of thiouracil in the gland might be expected to be greater after administration of iodothiouracil than after an equivalent dose of uniodinated thiouracil; a lower dosage could then be used, and the frequency of toxic effects would thus be reduced. It was also thought that the concurrent administration of iodine might diminish the hyperplasia and vascularity of the thyroid gland otherwise induced by the thiouracil; a reduction in the duration of pre-operative treatment would thus be possible and the technical difficulties of excision would be minimized.

Animal Experiments.—Experiments on rats and chicks have shown that the reduction in metabolism produced by iodothiouracil was quantitatively the same as that produced by thiouracil with or without the concurrent administration of potassium iodide (Barrett and Gassner, 1951). The thyroid histology of animals treated with iodothiouracil resembled the normal more closely than did that of animals treated with iodide and thiouracil singly or in combination (Barrett, Gassner, and Dittmer, 1951). Gassner *et al.* (1950) have also shown that iodothiouracil was less goitrogenic than thiouracil with and without iodide, and that it inhibited the goitrogenic action of exogenous thyrotrophic hormone, whereas thiouracil, alone or with iodide, augmented it.

Previous Clinical Trials

Reports on the use of this drug in over 190 patients have already been made from North America (Williams *et al.*, 1949; McClintock and Lyons, 1951; Catz *et al.*, 1951; Goldner and Kirschenfeld, 1952; Catz and Starr, 1953). The initial daily dosage varied from 50 to 800 mg., the optimum dosage appearing to lie between 200 and 400 mg., and the maximum clinical response was obtained in from eight to twenty-two days. Most workers found that some patients responded poorly; McClintock and Lyons (1951) believed that full remission was rarely produced. Definitive long-term therapy with iodothiouracil did not appear to be satisfactory owing to the incomplete and erratic control which was obtained; therefore the drug was mainly used in the preparation of patients for subtotal thyroidectomy. All these reports agree that the results obtained were from the surgical point of view satisfactory, the gland being less friable and vascular than after the usual preparation with a thiouracil derivative and iodine. Histologically, the glands appeared to be well involuted, and Catz and Starr (1952) reported that "in hyperthyroid patients prepared for operation with iodothiouracil, the thyroid epithelium has a lower average mean acinar cell height than in all the other treatment groups," which included groups treated with iodine alone and with iodine and a thiouracil drug together; in other words, the histology most closely resembled that of the normal gland in the group treated with iodothiouracil.

Present Investigation

Twenty-three patients with hyperthyroidism have been treated with sodium iodothiouracil ("itrumil"), 100 mg. of the drug containing 46 mg. each of iodine and thiouracil and 8 mg. of sodium. Eighteen patients were subsequently treated by subtotal thyroidectomy. The first seven patients were given 200 mg. of iodothiouracil daily, but as the condition of the glands at thyroidectomy was not so consistently satisfactory as had been expected the remaining patients were given 300 mg. daily. All patients were admitted to hospital and observed for seven to fourteen days before starting drug therapy; during this period of observation the diagnosis was confirmed clinically, by radio-iodine studies and by estimations of the basal metabolic rate (B.M.R.). The latter test was repeated on three successive mornings, the lowest of the three readings providing a more accurate indication of the level of thyroid activity than a single reading. During the periods of observation and treatment the pulse rate (including the sleeping rate) was noted, the patients were weighed twice weekly, and exophthalmometer readings, measurements of neck circumference, and white blood cell counts were made weekly.

A further group of six hyperthyroid patients admitted thereafter for preparation for subtotal thyroidectomy was observed in a similar way and was treated with methylthiouracil and potassium iodide concurrently in daily doses equivalent to those of the thiouracil and iodine in 300 mg. of iodothiouracil.

Clinical Effects

In most patients, between the third and eighth days of treatment, and usually on the fifth day, a change in the pattern of the pulse chart could be noted, the lowest pulse rate of the day (often the sleeping pulse rate) having fallen by about 10 beats, and the daily range of the pulse rate being also reduced, although to a less extent. This change commonly coincided with an improvement in the general condition of the patient and accompanied, or immediately preceded, an increase in weight. In almost all cases the increase in weight continued until the end of the three weeks' treatment which preceded operation or discharge from hospital. A further fall in the pulse rate was not so common, and in many cases the lowest level and the range of the daily pulse rate rose slightly towards the end of this period of observation; this phenomenon was probably associated with the increase in the patient's physical activity, which was encouraged before operation or discharge, although it may represent an escape from control by the antithyroid drug.

All but one of these patients gained weight during treatment with iodothiouracil, and during the first three weeks of treatment the average daily gain in weight was 5 oz. (140 g.), the gain being higher in those with diffuse goitre than in those with nodular goitre, and higher in those given 300 mg. of iodothiouracil daily than in those given 200 mg. daily.

Estimations of the B.M.R. provide a less reliable means of assessing progress, owing to the difficulty of producing a basal state in hyperthyroid patients. The average daily fall in B.M.R. during the first three weeks of treatment was about 1.5%, and again the average daily fall was greater in the patients with diffuse goitre than in those with nodular goitre, and greater in those treated with 300 mg. of iodothiouracil daily than in those treated with 200 mg. daily.

In none of the six patients treated for two months or more did an increase in the size of the goitre become obvious. Increase in exophthalmos did not occur during treatment in

any patient, but in two, following thyroidectomy, there was a temporary increase of 2 to 3 mm. accompanied by slight ocular discomfort. A transient maculo-papular rash developed in one patient, but disappeared without treatment being stopped. Agranulocytosis, leucopenia, or any other toxic effect was not observed.

Surgical and Histological Findings

All thyroidectomies performed on these patients were done by one surgical team. The surgeon was of the opinion that the glands of patients prepared for operation with iodothiouracil were firmer, less vascular, and less friable than the glands of patients who receive the usual preparation of a thiouracil drug *followed by* iodine. Particularly was there a reduction in the size of the surface veins of the gland, though periglandular adhesions seemed more dense. In half of the patients the condition of the gland was comparable to that found after preparation with iodine alone. The post-operative course in no case caused anxiety, and was usually uneventful.

Although in four of the seven patients treated with 200 mg. of iodothiouracil daily ideal technical conditions were found at thyroidectomy, in the others the results were not so satisfactory—the gland in one patient who received 200 mg. daily for only twelve days being as vascular and friable as the glands found in patients treated with thiouracil without iodine. It was on this account that the daily dose of iodothiouracil was increased to 300 mg.

Evidence of involution, with good colloid content, was found in most of the excised goitres. In two-thirds of the cases there was, however, some degree of hyperplasia, which was never extreme and was usually slight or moderate. In the remaining third the epithelial cells were cuboidal or flattened (Table I).

TABLE I.—*Summary of* 18 *Cases of Toxic Goitre Prepared for Surgery with Iodothiouracil*

Case No.	Age and Sex	Goitre	Lowest B.M.R. before Treatment	Iodothiouracil		Surgeon's Impression*	Histological Evidence of Hyperplasia
				Daily Dose	Duration in Days		
1	38 F	D	+16%	200 mg.	24	A	None
2	34 F	D	+54%	200 ,,	17	A	,,
3	46 F	N	+68%	200 ,,	12	C	Moderate
4	33 F	D	+45%	200 ,,	23	B	Marked
5	30 F	D	+53%	200 ,,	25	A	,,
6	34 F	D	+80%	200 ,,	30	A	None
7	53 F	D	+50%	200 ,,	27	B	Slight
8	47 F	N	+26%	300 ,,	22	A	Marked
9	51 M	D	—	300 ,,	60	A	None
10	28 F	D	+54%	300 ,,	25	B	Moderate
11	48 M	D	+50%	300 ,,	30	A	Slight
12	37 F	D	+46%	300 ,,	23	A	,,
13	55 F	N	+34%	300 ,,	23	B	,,
14	42 M	D	+48%	300 ,,	19	A	,,
15	46 F	D	+34%	300 ,,	19	B	Moderate
16	48 F	N	+17%	300 ,,	20	B	None
17	48 F	N	+55%	300 ,,	18	B	,,
18	50 F	D	+56%	300 ,,	18	B	Moderate

D=Diffuse. N=Nodular.
* Classification of surgeon's impression of condition of thyroid gland: A=comparable with glands after preparation with iodine alone; B=comparable with the more satisfactory glands after preparation with thiouracil followed by iodine; C=unsatisfactory—excessive vascularity and friability.

Long-term Treatment

One patient with hyperthyroidism complicated by auricular fibrillation and congestive heart failure was treated with 300 mg. of iodothiouracil daily for 60 days, during which time clinical improvement was continuous; at operation the condition of the thyroid gland was ideal, there being little increase in vascularity and no increase in friability or periglandular adhesions. Five patients have been treated with iodothiouracil for four months or more; in one patient with mild hyperthyroidism and exophthalmic ophthalmoplegia, although treatment was continued for nine months, good control of the hyperthyroidism was maintained, decrease in exophthalmos occurred, and there has been no relapse in the three months since treatment was stopped. In the four other patients who have been treated for from four to seven months control has not been so satisfactory, and iodothiouracil has been replaced, with benefit, by methylthiouracil in two patients.

Comparison with Patients Treated with Methylthiouracil and Iodine

The average daily gain in weight and the fall in B.M.R. were identical in the group of patients treated with equivalent doses of iodothiouracil and iodide. The condition of the thyroid at operation, from the point of view of vascularity and technical difficulty, was a little less satisfactory in the latter than in the iodothiouracil group, and histological evidence of hyperplasia was more frequent and more obvious (Table II).

TABLE II.—*Summary of Six Cases of Toxic Goitre Prepared for Surgery with Methylthiouracil and Potassium Iodide Concurrently, in Dosage Equivalent to* 300 *mg. Iodothiouracil Daily*

Case No.	Age and Sex	Goitre	Lowest B.M.R. before Treatment	Duration of Treatment in Days	Surgeon's Impression*	Histological Evidence of Hyperplasia
19	46 F	D	+28%	19	B	Moderate
20	39 F	N	+50%	25	C	,,
21	39 F	D	+26%	28	A	None
22	34 F	D	+10%	16	B	Moderate
23	33 F	D	+50%	22	B	,,
24	58 F	N	+26%	20	C	,,

* See footnote to Table I.

Discussion

In our experience iodothiouracil in daily dosage of 300 mg. for at least 17 days is a very satisfactory preparation for thyroidectomy in hyperthyroidism. A definite improvement in the clinical state occurs within a week of the start of treatment, there being thereafter a steady rise in weight of over 2 lb. (0.9 kg.) a week and a fall in B.M.R. of about 1.5% daily. The majority of patients are therefore fit for surgery within four weeks of starting iodothiouracil, and the field provided for the surgeon is technically satisfactory. It is thus possible to give all patients the advantage of an antithyroid agent in preparation without increasing the difficulties of the subsequent operation and without increasing appreciably the period of incapacity.

It is not so certain, however, that iodothiouracil possesses any new or distinctive features as a drug for the specific treatment of hyperthyroidism. The early clinical response, the tendency to escape from control after two to three weeks' treatment, and the difficulty in maintaining control in long-term treatment are suggestive of an iodine action, and it has yet to be shown that the iodine and thiouracil fractions of iodothiouracil act in the body in the organically combined form. It has been suggested that the studies of Plummer (1950) on the urinary excretion of the iodothiouracil are in favour of such an action, but the implications of these findings are doubtful.

Comparing the results of iodothiouracil treatment with those of methylthiouracil and iodine, we have been unable to show any significant difference beyond the impression that in the iodothiouracil group the operative field showed less excessive vascularity and the histological appearance was more commonly that of complete involution. Catz and Starr (1953), however, found that a shorter period of treatment was necessary to control hyperthyroidism with iodothiouracil than with thiouracil and iodine, that increase in goitre size occurred in the majority of patients treated with thiouracil and iodine but in none of those treated with iodothiouracil, and that the mean acinar cell height was lower in those treated with iodothiouracil, this signifying greater involution.

Astwood (1944) suggested that the actions of iodine and thiouracil in hyperthyroidism might be antagonistic, and that these drugs should therefore not be given simultaneously; it is in fact common practice in this country, when preparing

hyperthyroid patients for surgery, to discontinue the thiouracil two to three weeks before operation and to administer iodine alone for the remaining period (Rundle, 1951; Lange, 1953). However, Maxwell *et al.* (1946) and Williams (1946) reported satisfactory results with the concurrent administration of thiouracil and iodine. Rawson *et al.* (1945) believed that the iodinating and involuting actions of iodine are separate, and that, although the administration of the iodine does not result in the synthesis of thyroid hormone when iodine and thiouracil are given together, it does cause involution of the gland.

Conclusion

Although the number of cases observed in the present series is small we believe that the use of concurrent thiouracil and iodine (whether given as iodothiouracil or as methylthiouracil with potassium iodide) is a most satisfactory method of preparing for operation patients with moderate or severe hyperthyroidism. Those patients with mild hyperthyroidism who require operation are adequately prepared with iodine alone. Preparation with concurrent thiouracil and iodine is more rapid and produces a more satisfactory surgical field than does preparation with thiouracil followed by iodine. In cases of moderate severity the relatively slight increase in the duration of pre-operative treatment, compared with the duration of pre-operative treatment with iodine alone, is fully justified by the increased degree of safety obtained.

Summary

The literature concerning iodothiouracil, an organic combination of iodine with thiouracil, is reviewed, and a further clinical trial of this drug is reported.

Twenty-three patients suffering from hyperthyroidism, 18 of whom had subsequent thyroidectomies, were treated with iodothiouracil in doses of 200 to 300 mg. daily for periods of 12 days to 7 months.

The reduction in hyperthyroidism and the involution produced in the thyroid gland of patients prepared for surgery were most satisfactory; the results of prolonged medical treatment with iodothiouracil were variable.

It is doubtful whether the pharmacological properties of iodothiouracil differ from those of the constituent iodine and thiouracil fractions when the latter are administered at the same time.

Our thanks are due to Ciba Laboratories, Ltd., for the generous supplies of itrumil and to the Pathological Department of St. Bartholomew's Hospital for the preparation of the microscopical sections.

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The National Gastroenterological Association announces that the name of its official publication, established in 1934, has been changed from *The Review of Gastroenterology* to *The American Journal of Gastroenterology*. There has been no change in the editorship. An earlier journal of this name was published from 1911 to 1914 by the American Hospital for Diseases of the Stomach, Philadelphia.

LONG-TERM THERAPY OF THYROTOXICOSIS WITH THIOURACIL COMPOUNDS

BY

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Now that the treatment of thyrotoxicosis by thiouracil compounds has been in use for a number of years, it is becoming possible to determine its long-term effects and, in particular, the conditions under which this therapy is likely to be most successful. Most of the earlier contributions to this aspect of the subject have been reviewed by Astwood (1949), and accounts of more recent investigations have been published by Himsworth (1948), Williams (1949), Dunlop and Rolland (1950), Trotter (1950), Poate (1950), Wing and Asper (1952), and Douglas and Kennie (1952).

The present report is a summary of observations which began in 1944 at the Sheffield Royal Infirmary on the effects of treating thyrotoxicosis by means of thiouracil compounds. The inquiry was planned with a view to throwing light on three main questions which are of special interest to the medical practitioner: (*a*) How successful are these drugs in initially controlling the signs and symptoms of this disease? (*b*) To what extent can control be maintained over long periods by continuous administration of maintenance doses of the drug? (*c*) What are the chances of relapse after maintenance treatment is withdrawn? In particular, is length of remission after withdrawal related to such factors as the age of the patient, length of his illness, and the duration of his treatment before withdrawal?

Procedure

A total of 126 patients with typical signs and symptoms of thyrotoxicosis were treated for varying periods of up to six years with thiouracil, methylthiouracil, or propylthiouracil, according to the scheme already described in previous communications (Wilson, 1946; Wilson and Goodwin, 1947). As was pointed out previously, we have found that, though propylthiouracil was not superior to methylthiouracil, both compounds were less apt than thiouracil to produce toxic effects, and that the therapeutic response was favourable in either type of thyrotoxicosis. For the purpose of the present analysis no attempt is made to distinguish patients with primary from those with secondary thyrotoxicosis, or to differentiate between them according to severity of the disease, presence or absence of specific symptoms, the particular thiouracil compound and dose used, and the length of treatment needed before initial control was achieved. "Initial control" was assessed by the criteria previously described (Wilson, 1946). All patients who were controlled initially were given maintenance treatment, and from 94 of these it was subsequently withdrawn

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after varying periods of treatment. The decision to withdraw it from individual patients who were satisfactorily controlled was made arbitrarily and without regard to their age and previous history.

Results and Discussion

Initial Control.—Fig. 1 shows that of the 126 patients treated with thiouracil compounds 113, or 90%, were initially controlled, usually after three to six weeks of treatment. From the remaining 13 patients (10%) the drug was withdrawn without initial control having been established: 6 of these showed no signs of responding to the drug, 3 developed leucopenia, and 4 developed drug fever and nausea.

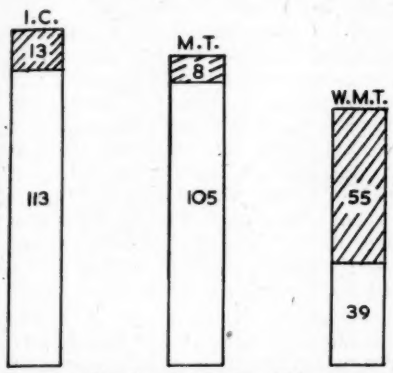

FIG. 1.—Results of treating 126 patients with thyrotoxicosis by thiouracil compounds. White columns = Satisfactory. Cross-hatched columns = Relapsed. I.C. = Initial control. M.T. = Maintenance therapy. W.M.T. = Withdrawal of maintenance therapy.

Maintenance Therapy.—Of the 113 patients who had been controlled initially, 105 were treated with maintenance doses for periods ranging from 3 to 62 months (mean = 18.0, S.D. = 12.9). Treatment of the remaining eight patients had eventually to be discontinued because two developed leucopenia five and fifteen months respectively after beginning treatment, one became drug resistant after two years, and five were referred for thyroidectomy on account of increasing thyroid enlargement.

Withdrawal of Maintenance Therapy.—Treatment was withdrawn from 94 of the 105 patients who had been on satisfactory maintenance for periods ranging from 2 to 55 months (mean = 17.1, S.D. = 12.2). Of these, 55 eventually relapsed at various times after withdrawal (relapsed group), while 39, at the time of the last interview, were still in remission after periods which ranged from 3 to 47 months since withdrawal of therapy (satisfactory group).

Factors Influencing the Incidence and Onset of Relapse

In an attempt to determine what factors might influence a patient's response to withdrawal of maintenance therapy, the two groups (satisfactory and relapsed) were compared with respect to four characteristics which a survey of the literature had suggested as relevant. These were: (1) age at first interview; (2) length of illness; (3) length of treatment before drug withdrawal; and (4) length of remission after withdrawal. It will be appreciated, however, that our satisfactory group includes patients who have been observed for only short periods and therefore may yet relapse.

In Table I it will be seen that the two groups were equally matched in respect of the patient's age and length of treatment before withdrawal of the drug. The mean length of previous illness in the relapsed group, however, was approximately double that of the satisfactory group, but the scatter is very wide and the difference between the means is not statistically significant.* It is of interest to note that the standard deviation of length of illness in the relapsed group is also double that in the satisfactory group, indicating that the relapsed group has included a greater proportion of patients with illness of very short and of very long duration. The mean length of remission—that is, relief from signs and symptoms after withdrawal of maintenance therapy—is much less in the relapsed group (8.7 months) than in the satisfactory group (24.5 months). The difference between these two means is highly significant ($P<0.001$). This suggests that if relapse is to occur it tends to do so fairly soon after treatment is withheld. This is confirmed by Fig. 2, which shows the distribution of length of remission following withdrawal of treatment. It will be seen that 49 out of 55 relapses occurred within the first fifteen months after withdrawal and, further, that of 33 patients with remissions of between 15 and 48 months only 6 have so far relapsed.

TABLE I.—*Summary of Age, Length of Illness, of Treatment, and of Remission of 94 Patients from Whom Maintenance Therapy had been Withdrawn*

	Satisfactory (39)			Relapsed (55)		
	Range	Mean	S.D.	Range	Mean	S.D.
Age at interview (years)	13–73	45·48	14·31	19–69	44·02	11·58
Length of illness (months)	1–44	23·41	29·96	1–240	42·22	58·15
Length of treatment (months)	2–55	16·13	10·97	2–54	17·75	12·97
Length of remission after withdrawal of treatment (months)	3–47	25·54	13·56	1–35	8·67	7·54

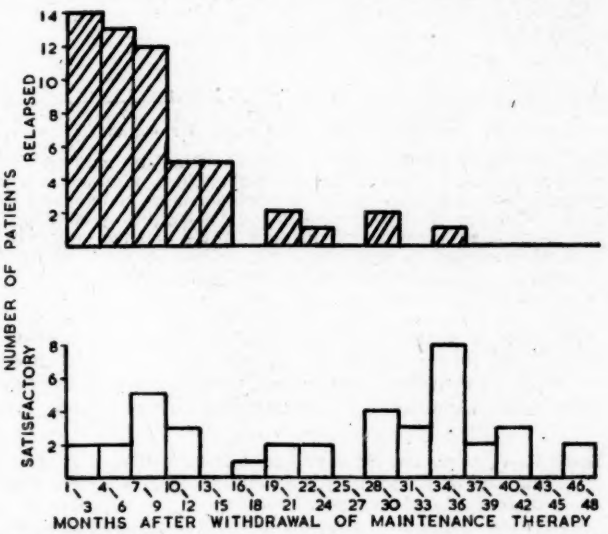

FIG. 2.—Distributions of relapsed and satisfactory patients in relation to time after withdrawal of maintenance therapy.

The liability to relapse after the withdrawal of treatment can be determined more precisely by arranging the data in the form of a life-table and calculating the probability of an individual relapsing within any given period after withdrawal (Fig. 3). It will be seen that the risk of relapsing is greater within 15 months or so from withdrawal of treatment, and thereafter does not increase greatly. The shape of the curve suggests that not many more relapses are likely to occur after the end of the 36th month following withdrawal. On the basis of our data, the overall probability of relapsing within 48 months after withdrawal of treatment (the maximum time that any of these subjects have been observed) is about 0.66; in other words, the odds are 2 to 1 that a patient will relapse within this period. These results are similar to those of Trotter (1950), except that he found the overall chances of relapse to be about 0.5—rather lower than ours. As he has pointed out, however, since the number of patients studied becomes progressively less, the later parts of this kind of probability curve are less reliable than the earlier. In view of this and the relatively small number of cases involved in each investigation (about 100), the difference between his figure and ours is probably to be attributed to sampling fluctuations.

*In view of the non-normality of the distributions and the discrepancy between the standard deviations, the proportions of satisfactory and relapsed patients above and below the median were compared by a χ^2 test. The results were in agreement with the tests on means.

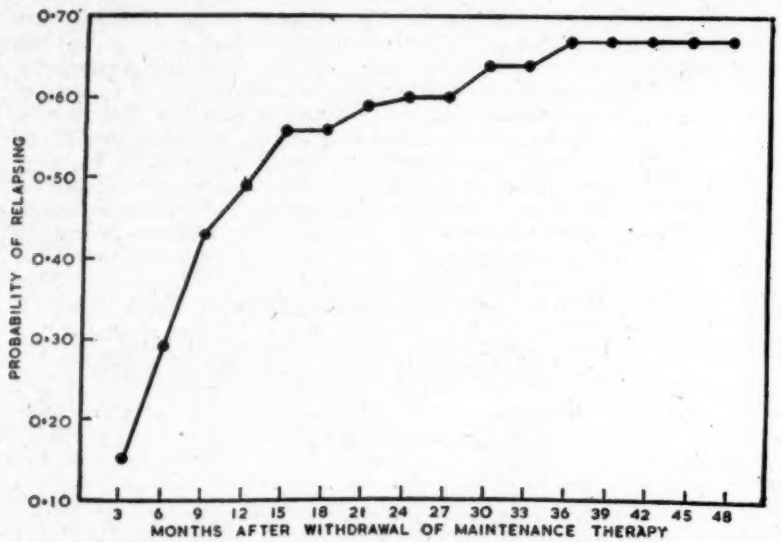

FIG. 3.—The probability of relapsing in relation to time after withdrawal of maintenance therapy. In calculating the probabilities, allowance has been made for the fact that the satisfactory patients who had been in remission for only a limited period when the observations ended could subsequently be expected to relapse. To fail to make an allowance of this kind would bias the table. It has, furthermore, been assumed that all satisfactory cases were "at risk" for half the three-months period in which they ceased to be observed.

In order to examine further whether length of remission was related to the age of the patient, length of his illness, or length of treatment, correlations were calculated between these four variables for the relapsed group (Table II).

TABLE II.—*Correlations Between Age, Length of Illness, of Treatment, and of Remission for 55 Patients who Relapsed After Withdrawal of Maintenance Therapy*

	Length of Illness	Length of Treatment	Length of Remission
Age of patient	+0·064	−0·040	−0·208
Length of illness ..		−0·144	−0·058
„ „ treatment ..			−0·264

There was no point in calculating similar correlations for the satisfactory group, because for them the length of remission could not be finally determined. As a result, information concerning a number of patients with long and possibly permanent remissions, who from the practitioner's point of view are perhaps the most interesting of all, could not be taken into account. For this reason the correlations we have calculated, using data from the relapsed group only, do not give a complete picture.

It will be seen from Table II that the correlations are all very small. The only one which approaches statistical significance at the 5% level is between length of treatment and length of remission. The correlation is negative, suggesting a possible tendency for longer treatments to be associated with shorter remissions. This is contrary to what might be expected on the basis of previous reports that, if treatment was maintained for longer periods, the patient tended to take correspondingly longer to relapse (Himsworth, Morgans, and Trotter, 1947; Himsworth, 1948; Dunlop and Rolland, 1950). Douglas and Kennie (1952) have shown that the proportion of patients who relapse is much greater among those who have had treatments of less than one year before withdrawal than among patients who have been treated for one to two and a half years or more. However, inspection of their figures also suggests that, of the patients who do relapse, those who have had treatments of one year or longer tend to relapse sooner—in half the time, on an average—than those who have been treated for periods of less than one year. Our own observations provide some striking examples of patients with long remissions following short treatments; seven patients, for instance, whose treatments were nine months or less were still in remission more than three years after treatment had been withdrawn. Furthermore, out of 12 patients treated for two and a half years or longer, only 2 have not yet relapsed, and in every case the relapse occurred well under twelve months after withdrawal of treatment.

Himsworth (1948) found that in patients with remissions of over two years after withdrawal of the drug the average duration of treatment had been 15 months (S.D.=6.3). This agrees well with our own figures, where the corresponding average for 23 patients with remissions of over two years is 17.6 months (S.D.=8.8). But since this figure is almost identical with the average length of treatment for the whole of our relapsed group (17.8 months, S.D.=13), length of treatment in our sample of patients, at any rate, clearly cannot be used to discriminate between short and long remissions.

The correlation between age of patient and length of remission, though not statistically significant, is negative—suggesting a possible tendency for longer remissions to be more common in younger patients—which is probably what one would expect.

The length of the patient's illness before treatment does not seem to be significantly associated with the length of his remission after withdrawal of treatment. This, however, may not be the case with thyrotoxicosis of several years' standing; for example, out of 13 of our patients who had been ill for more than four years only one had not relapsed at the time of the last recorded interview, and 10 of the 12 who relapsed have done so after remissions lasting only a few months. This high relapse rate among the patients with very long illnesses seems to be the main reason for the discrepancy between the mean length of illness of the relapsed and that of the satisfactory group (Table I).

That there should be no correlation in our sample of patients between length of treatment and age or length of illness is, of course, what might be expected, since length of treatment for each patient was determined at random.

In view of the relative lack of association between length of remission and the three factors which we have examined above, it seems reasonable to conclude that other influences, such as intercurrent infection and social maladjustment (Douglas and Kennie, 1952), may be more relevant in determining a patient's response to withdrawal of maintenance therapy with thiouracil compounds.

Summary

Of 126 patients with thyrotoxicosis who were treated by thiouracil compounds 90% were initially controlled.

Of 113 patients who were continued on maintenance therapy for periods from three to sixty-two months, 105 remained in remission during such treatment.

Maintenance therapy was withdrawn from 94 of the patients after periods of treatment ranging from 2 to 55 months, and 55 relapsed. It has been shown that the probability of relapsing is greatest within about 15 months after withdrawal of treatment. After 36 months the chances of relapsing are slight. On the basis of these figures it has been calculated that approximately two out of every three patients will eventually relapse after withdrawal of treatment.

No consistent relation has been found between the length of the patients' remission and their age, the

duration of their illness, and the duration of treatment. It is concluded that other factors may determine a patient's response to withdrawal of maintenance therapy with these drugs.

We wish to thank Professor E. J. Wayne for the opportunities of studying the cases under his care and the physicians of Sheffield Royal Infirmary for their valuable co-operation. We also wish to thank Dr. A. G. MacGregor for his help and for supplying data on the follow-up of some of the patients, and Mr. Arthur Summerfield for helpful advice on the statistical analysis. Part of the expenses of this research were defrayed by a grant from the Medical Research Council to one of us (A. W.) and to another (H. S.) who is in receipt of a whole-time personal grant.

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MILK, *p*-AMINOBENZOATE, AND MALARIA OF RATS AND MONKEYS

BY

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This paper describes investigations concerning the effect of milk diets upon the course of malarial infections, and the supplementation of such diets by *p*-aminobenzoate, which is a growth factor for many species of plasmodia.

In 1952 Maegraith, Deegan, and Jones reported that infections of *Plasmodium berghei* do not develop properly if the hosts (rats) are maintained on a milk diet. A preliminary communication from this laboratory (Hawking, 1953) pointed out that a milk diet was deficient in *p*-aminobenzoate, which is apparently needed by many plasmodia. It was shown that if *p*-aminobenzoate was added to the milk diet the infection of *P. berghei* developed normally, and it was concluded that *p*-aminobenzoate (or some derivative) is a growth factor for *P. berghei*. According to our conception the body fluids of animals usually contain very little *p*-aminobenzoate (otherwise sulphonamides would not be therapeutically effective against so many bacteria); *p*-aminobenzoate is present in many diets; when ingested in the food it raises the blood concentration sufficiently for malaria parasites to grow; and it is rapidly excreted or destroyed, so that constant renewal is necessary. The interrelationship of growth factors and malarial infections raises so many questions, both practical and academic, that several years will be needed to investigate them adequately. As, however, the subject is of interest to other workers, the results obtained to date are presented here.

Plasmodium berghei in Rats

The animals employed were obtained from the strain of piebald rats maintained at this institute. After preliminary experiments it was found that rats weighing 200 g. were preferable to those of 100 g. or 50 g., because with the smaller weights suppression of the infection by milk diet was more difficult to demonstrate. The normal diet of these rats is a stock laboratory one which has been described by Bruce and Parkes (1949). Briefly, it contains wholemeal flour 46%, Sussex ground oats 40%, white fish meal 8%, dried skimmed milk 3%, dried yeast 1%, cod-liver oil 1%, and salts 1%. The milk employed was obtained from the ordinary dairy, and had been pasteurized. One sample of it was found by bioassay (kindly performed by Dr. A. T. Fuller) to contain 3.1 mμg. free and 19 mμg. total *p*-aminobenzoate per ml. The rats were housed three in a cage over a grid to allow escape of faeces. They were supplied with milk from a bottle. The bottles were changed morning and evening, and they were autoclaved in between each change. The quantity of milk was limited to the amount which the rats would probably consume in four to five hours, and all other possible steps were taken to prevent the milk going sour. The rats were placed on the diets for two to four days before inoculation. The strain of *P. berghei* was the RSVP strain obtained from Professor P. C. C. Garnham. The inoculum usually contained about 2 million parasitized cells per rat, and it was injected intraperitoneally. The degree of infection was expressed as the number of parasitized red blood corpuscles in a thin stained film per microscope field; this usually contained about 200 corpuscles.

The result of a typical experiment is shown in Fig. 1, in which the intensity of infection in each cage of three rats is shown as the mean of the logarithms of the number of

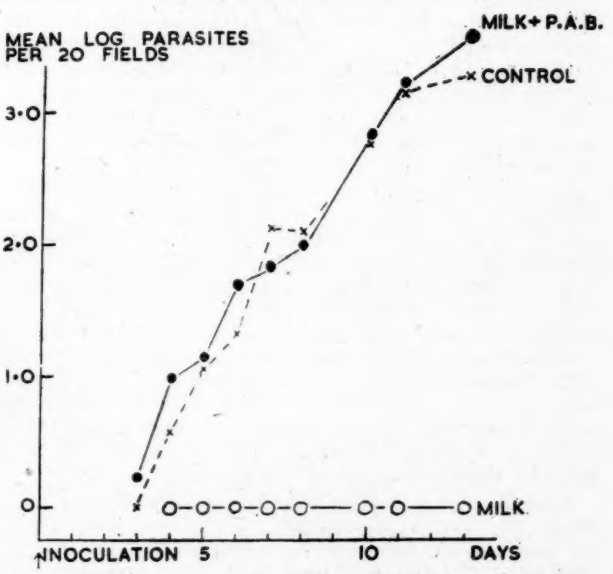

FIG. 1.—The development of *P. berghei* in rats on milk diet, milk plus *p*-aminobenzoate (P.A.B.) 1/40,000, and stock diet. Each line represents the mean of the logarithms of three rats, the infections being expressed as the number of parasitized cells per 20,000 erythrocytes. Inoculation intraperitoneally on Day 0 with 100,000 parasitized cells per rat. Weight of rats, 190–220 g.

parasitized erythrocytes per 20,000 cells in a thin blood film. (For this calculation, animals which showed no parasites were deemed to have 1 per 20,000 cells; animals dying of the infection towards the end of the experiment were deemed to have 8,000 parasites per 20,000.) This figure shows that the infection of *P. berghei* does not develop in rats on a milk diet (confirming the report of Maegraith *et al.*), but that if *p*-aminobenzoate is added to the milk the infection develops as well as in the control rats on the complete laboratory diet.

In order to obtain suppression of the infection on milk diet various precautions are necessary. Thus the rats employed should be fully adult—that is, weighing 200 g.—in younger rats the suppression is more difficult to obtain. The

milk must not be allowed to become sour; presumably souring is accompanied by increase of the *p*-aminobenzoate content. Prolongation (beyond three to four days) of the period on the diet before inoculation did not seem greatly to improve the results.

Probably this suppression of infections of *P. berghei* by milk diet is a marginal phenomenon, and a small alteration of the conditions may make the difference between success and failure. The composition of milk, including its content of *p*-aminobenzoate, is not uniform, but will vary according to the season and diet of the cows; at some seasons it was difficult to demonstrate suppression of parasitaemia by milk diet. It was sometimes observed that in two of a group of rats on milk there was complete suppression of parasitaemia, while in the third rat the infection was as great as in the controls; such a result suggests some individual factor present in certain rats, possibly different bacterial flora or syntheses in the intestine.

In some experiments chloramphenicol 1/20,000 was added to the milk in the hope of reducing bacterial growth in the intestine and thus diminishing a factor which might interfere with the effect of the milk diet; in such experiments, however, the malarial infection developed almost as well as in the control rats on a complete diet—that is, the suppression of the malaria by milk diet was *reversed*. This result was surprising, until it was learnt that chloramphenicol can be decomposed by *Bact. coli* and other bacteria into various derivatives which include *p*-aminobenzoate (Smith, 1953).

The minimum concentration of *p*-aminobenzoate in milk required to permit growth of *P. berghei* as good as in the controls seemed to be about 1/40,000; concentrations of 1/100,000 and 1/1,000,000 were sometimes effective and sometimes not. Assuming that each 200-g. rat consumes 150 ml. of milk a day, a concentration of 1/40,000 corresponds to a daily intake of approximately 20 mg. of *p*-aminobenzoate per kg. body weight.

Rats on a milk diet sometimes get diarrhoea, indicating modification of the intestinal flora. Rats on the control diet lost on an average 5% of weight in two weeks during the experiments, presumably owing to the malaria; on a milk diet they lost 2–3%. Pteroylglutamic (folic) acid 1/10,000 added to the milk promoted the growth of *P. berghei* as well as an equimolar solution of *p*-aminobenzoate—that is, 1/40,000; accordingly, these two compounds seem to be interchangeable, but it is not clear which of them is converted into the other. The suppression of *P. berghei* by milk diets could not be reversed by adding methionine (1/2,000) or *p*-hydroxybenzoate (1/3,000) to the milk or by injecting vitamin B_{12} (150 μg. per kg. daily).

Infection by *P. berghei* could also be prevented from developing by placing the rats on other deficient diets—for example, a grossly deficient one consisting only of 10% glucose. Rats live well on this diet for over two weeks (end of experiment), with a loss of weight averaging 6–24% in different experiments. Addition of *p*-aminobenzoate 1/1,000 plus methionine 1/500 to this diet was not enough to allow the infection to develop.

Suppression of *P. berghei* infection by milk diet could also be demonstrated in mice, but often the suppression was less complete than that observed in rats.

Plasmodium knowlesi in Monkeys

The suppression of *P. berghei* infections by the administration of a *p*-aminobenzoate-deficient diet—for example, milk—can be correlated with the great susceptibility of this parasite to sulphonamides (which antagonize *p*-aminobenzoate). Accordingly experiments were made to ascertain whether the same phenomenon (suppression by milk diet and reversal by *p*-aminobenzoate) could be demonstrated with other malarial infections known to be sensitive to sulphonamides. The first study was made with *P. knowlesi*, which is known to respond readily to sulphonamide treatment. The strain was derived from the new and virulent strain recently isolated by Edeson (Edeson and Davey, 1953). Four small *Macaca mulatta* monkeys weighing approximately 1.5 kg. were placed as follows:

Monkey 224 on the normal complete laboratory diet, as used for rats.
Monkey 225 on milk.
Monkey 226 on milk plus *p*-aminobenzoate 1/10,000.
Monkey 227 on milk plus *p*-aminobenzoate 1/1,000,000.

After three days, each of them was inoculated intramuscularly and intraperitoneally with 5×10^7 parasitized blood corpuscles. The course of the resultant infections is shown in Fig. 2. (The infection in Monkey 226 was indistinguishable from that in Monkeys 224 and 227 and has been omitted.)

Briefly the control Monkey 224 showed parasites in the blood five days after inoculation, and the next day it was treated with mepacrine and sulphadiazine to save its life. Monkey 225 (on milk) never showed any parasites during five weeks while it was fed only on milk; four days after it had been transferred to a normal diet its blood contained one parasite in every microscope field. Clearly the infection had been kept at a level too low for recognition while the monkey was on the milk diet, but the parasites multiplied rapidly when a complete diet was given. Monkey 227 (on milk plus *p*-aminobenzoate 1/1,000,000) and also Monkey 226 (milk plus *p*-aminobenzoate 1/10,000) showed the development of parasitaemia indistinguishable from that of the control monkey (224). Monkey 227, weight 2 kg., consumed about 1 litre of milk a day, so that it received about 0.5 mg. of *p*-aminobenzoate per kg. daily; this small amount was apparently enough to make it fully susceptible to infection with *P. knowlesi*. As the supply of monkeys was limited and the results formed such a striking confirmation of expectations, the experiment was not repeated. Possibly with a larger group of monkeys on milk diet the suppression of parasitaemia would not always have been so complete.

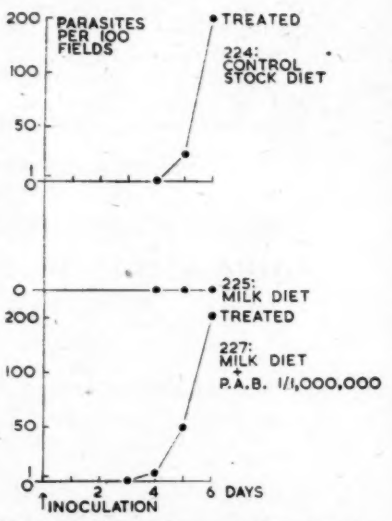

FIG. 2.—The development of *P. knowlesi* in monkeys on milk diet, milk plus *p*-aminobenzoate 1/1,000,000, and stock diet. The infection is expressed as the number of parasites per 100 microscope fields each containing approximately 200 erythrocytes.

Similar experiments were made with *P. cynomolgi* in monkeys and yielded similar results; they are described later in this paper. Preliminary attempts were made to keep chickens on diets of liquid milk or dry milk so as to test *P. gallinaceum* (which is also sensitive to sulphonamides). The chickens did not take well to the diets, and the effects upon the infection were not clear. Further experiments with *P. gallinaceum* were postponed.

Malaria in Baby Animals

As pointed out by Maegraith *et al.*, the suppression of malaria infections in laboratory animals by milk diet raises the interesting question whether a similar suppression may occur in human babies in the Tropics while fed exclusively on breast milk. Certainly *P. falciparum* and *P. vivax* are sensitive to sulphonamides, and so presumably they require *p*-aminobenzoate. Model experiments were made on young laboratory animals.

(a) Suckling Rats Inoculated with P. berghei

Litters of rats about one week old were taken when the baby rats weighed about 10–15 g., and were tested as shown in the Table. In this experiment the babies (eight in each cage) were inoculated intraperitoneally each with 1 million parasitized cells (Day 0). The mothers were placed on a

Development of P. berghei in Suckling Rats Receiving p-aminobenzoate (P.A.B.) by Different Routes

Cage	Contents	Mean Parasitaemia			
		4 Days	5 Days	6 Days	7 Days
1	Controls ..	4·6 (3/8)	13 (4·8)	51 (6/8)	126 (8/8)
2	Babies inoculated with 0·1 mg. P.A.B. i.p.	2,000 (8/8)	3,400 (8/8)	—	2,800 (8/8)
3	Mother smeared with P.A.B.	1,250 (8/8)	2,400 (8/8)	—	3,100 (8/8)
4	Mother inoculated with 10 mg. P.A.B. i.p.	2,000 (8/8)	4,000 (8/8)	—	3,500 (8/8)
5	Young rats (50 g.) on stock diet		1,000 (4/4)	3,000 (4/4)	

Mean parasitaemia is expressed as the geometric mean of the number of parasitized erythrocytes per 20,000 cells. The figures in brackets indicate the proportion of animals showing parasites.

diet of 4 parts starch plus 1 part casein, beginning on the day before the experiments in order to diminish the amount of *p*-aminobenzoate in their diet. In cage 2 the baby rats were inoculated intraperitoneally twice daily with 0.1 mg. of *p*-aminobenzoate each; in cage 3 a mixture of 10% glucose plus 1% *p*-aminobenzoate was smeared on the nipples of the mother twice daily, so that the babies would receive the compound when they sucked; in cage 4, 10 mg. of *p*-aminobenzoate was injected intraperitoneally twice daily into the mother (200 g. weight) with the expectation that some would be excreted in the milk. Cage 5 contained four young rats (50 g.) on stock diet as an extra control. When the blood of these baby rats was first examined four days after inoculation, only three out of the eight controls (cage 1) showed scanty parasites. By seven days all the controls showed parasites, but their numbers were few. Cage 5 (weaned rats on stock diet) showed the usual acute infection developing. In all the three litters which received *p*-aminobenzoate by any route (cages 2, 3, and 4), the infection was already almost at its maximum level even on the fourth day. The fact that this occurred even in the babies of the mother receiving *p*-aminobenzoate by injection (cage 4) confirms the expectation that *p*-aminobenzoate (or a derivative) is excreted in the milk.

This experiment (which is typical of others) shows that infections of *P. berghei* in suckling rats develop much more rapidly and intensely if *p*-aminobenzoate is supplied by some route or other; from which it may be concluded that in normal circumstances the malarial infection is held back by a deficiency of this subject. Theoretically, suckling rats on a diet completely deficient in *p*-aminobenzoate would be insusceptible to infection; in practice suckling rats probably receive a small amount of *p*-aminobenzoate in their mother's milk, derived from her diet or perhaps from her intestinal bacteria, and this is sufficient to account for the low-grade infection which develops. The more stringent the precautions taken to exclude *p*-aminobenzoate from the diet of the mothers, the greater the suppression of parasitaemia in the babies. Thus in some experiments the mother rats were placed on *p*-aminobenzoate-deficient diet (starch 80%, casein 20%), beginning three days before parturition, and the babies were inoculated with malaria three days after they were born; babies of mothers which received *p*-aminobenzoate by twice-daily injection developed a parasitaemia of about 1% in five days, and the parasitaemia rapidly increased; babies of mothers not receiving *p*-aminobenzoate remained free from parasitaemia for 13 days and many of them never developed infection. If, on the other hand, the laboratory diet of the mother rats was rich in *p*-aminobenzoate, it might probably be impossible to demonstrate the above insusceptibility of sucklings to malaria.

(b) Baby Monkeys and P. cynomolgi

A few young *M. mulatta* monkeys were available from breeding at this institute. Two of these were about 1 month old, receiving milk from the breast or a bottle, and the others were 5 to 14 months old and had been weaned on to ordinary diet.

In the first experiment there were four monkeys as follows:

Monkey 217, weighing 3.8 kg., fed on the normal laboratory diet (food cubes as for rats and also occasional cabbage).

Monkey 221, weighing 3.5 kg., on milk diet.

Monkey 222, over 1 year old, weighing 2.5 kg., placed on a diet of milk plus *p*-aminobenzoate 1/1,000.

Monkey 223, 4 weeks old, weighing 0.75 kg. It had been brought up on milk from a bottle because its mother had refused to feed it. It had also received 9 ml. daily of a vitamin preparation called "haliborange." (This contains 75 mμg. of *p*-aminobenzoate per ml.: Dr. A. T. Fuller.)

After Monkeys 217, 222, and 223 had been on their diets for one week, and 223 was 4 weeks old, all were inoculated intraperitoneally and intramuscularly with blood containing about 2×10^7 parasites of *P. cynomolgi*. The infections in 217, 221, and 222 are shown in Fig. 3. Monkey 217 (control on full diet) showed a typical infection with this parasite. Monkey 221 (on milk diet) showed no parasites for 10 days; it was then placed on milk plus *p*-aminobenzoate 1/1,000, but no parasites appeared during the next nine days; it was then inoculated with blood containing *P. cynomolgi* (to demonstrate its susceptibility), and a typical infection developed. Monkey 222 (on milk plus *p*-aminobenzoate 1/1,000) developed a typical infection, similar to that of the control (217) but rather more severe. Monkey 223 showed no parasites until the fourteenth day, when two rings were discovered in 50 fields; on the fifteenth day the infection was six per 50 fields; on the sixteenth day it was three per 50 fields, and on the seventeenth it was one per 100 fields. On the fifteenth day it was discovered that the monkey had received 9 ml. of haliborange daily from the sixth day onward, which would contribute 0.6 μg. of *p*-aminobenzoate per day; this was stopped. On the nineteenth day one parasite was seen in 50 fields. The monkey ceased to gain weight, and put its hand to its head as though it had headache. On the twenty-second day it was put on chloroquine treatment (15 mg. per kg. daily intramuscularly for three days) and no further evidence of malaria has been seen.

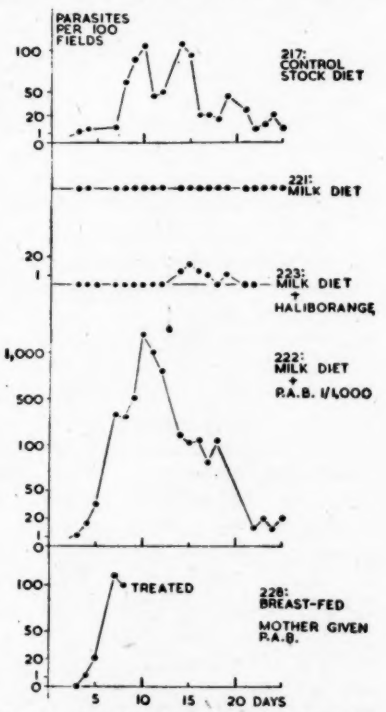

FIG. 3.—The development of *P. cynomolgi* after inoculation with infected blood of monkeys on various diets, as described in the text. The infection is expressed as the number of parasites per 100 microscope fields, each containing 200 erythrocytes; for numbers above 100 the scale is greatly reduced for convenience.

The results with Monkeys 217, 221, and 222 show that a milk diet suppresses blood-induced infections of *P. cynomolgi* and that this suppression is reversed by *p*-amino-

benzoate. In the baby monkey (223) suppression was incomplete, although the parasitaemia was very much later and lower than in the control (217). This incompleteness of suppression may have been due to variation between different animals, or it may have been due to the haliborange preparation.

Fig. 3 also shows an experiment with another monkey (228) which was performed on a later occasion but which is added here for ease of comparison. This was a baby rhesus monkey, 10 weeks old, which was being nursed on its mother's breast. (In a previous experiment—see below—it had been inoculated twice with sporozoites of *P. cynomolgi* and no infection had developed.) The mother was inoculated intramuscularly twice daily with *p*-aminobenzoate, 0.03 g. per kg.

After this had been done for six days the baby (228) was inoculated intraperitoneally with approximately 3×10^6 parasites of *P. cynomolgi*. Parasites appeared in the blood after four days and reached the stage of two parasites per field seven days after inoculation (after which the monkey was treated). As shown in Fig. 3, the development of infection in this monkey was similar to that of the previous control monkey (217) and of the monkey receiving *p*-aminobenzoate as well as milk (222). This experiment confirms the previous experiments with rats, demonstrating that when *p*-aminobenzoate is administered to nursing mothers it (or a derivative) passes via the milk to the offspring and renders them susceptible to malarial infection.

In the second type of experiment, infection was induced by means of sporozoites of *P. cynomolgi*. There were four *M. mulatta* monkeys:

Monkey 218 was kept on normal diet as a control.

Monkey 229, weight 3.8 kg., was placed on milk diet.

Monkey 230, weight 2.2 kg., was placed on milk plus *p*-aminobenzoate 1/5,000.

Monkey 228, a baby on the breast (mentioned above), was 4 weeks old when inoculated.

After 229 and 230 had been on their diets for five days all four monkeys were inoculated intraperitoneally with a suspension containing the glands of one infected mosquito—that is, each monkey received one-quarter of this amount; 20 days later this inoculation was repeated for each monkey. The results with three of the monkeys are shown in Fig. 4. Briefly, 218 first showed parasites 14 days after the first inoculation, and the infection reached a peak of 10 parasites per field on the twenty-second day; this is a typical infection following the inoculation of small numbers of sporozoites of *P. cynomolgi*. Monkey 228 (breast-fed baby) showed no parasites during eight weeks from inoculation, after which it was used for another experiment. Monkey 229 (on milk diet from a bottle) showed no parasites for five weeks. It was then placed on the normal diet again. Eighteen days after this change it began to show parasites, and mild parasitaemia (maximum 19 parasites per 50 fields) persisted for five days. (As the graph of this monkey was indistinguishable from that of 228 it has been omitted from Fig. 4.) Monkey 230 (milk plus *p*-aminobenzoate) showed parasites 14 days after the first inoculation and experienced an infection indistinguishable from that of the control (218).

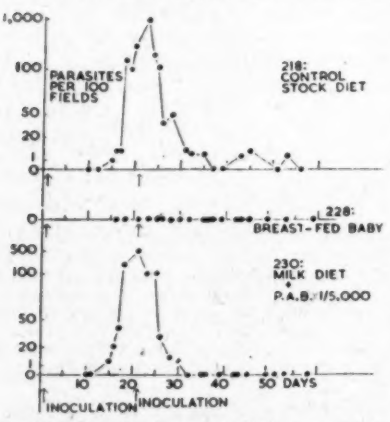

FIG. 4.—The development of *P. cynomolgi* after inoculation of sporozoites (on two occasions) in monkeys on diets of breast milk, cow's milk plus *p*-aminobenzoate 1/5,000, and stock food cubes. The infection is expressed as in Fig. 3.

This work shows that infections of *P. cynomolgi* induced by sporozoites are suppressed by a milk diet, and that again this suppression is reversed by *p*-aminobenzoate. Bray and Garnham (1953) have previously shown that the pre-erythrocytic forms are not abolished by the milk diet; they persist in a latent form, and the infection breaks out again when the animal is returned to a normal diet. The absence of parasitaemia in the breast-fed baby (228) is particularly suggestive as an explanation of the partial insusceptibility of human infants to malaria.

Discussion

In the above work and the papers already quoted it is shown that milk (and other) diets render rats and monkeys insusceptible to infection with malaria, and that this insusceptibility may be due to a deficiency of *p*-aminobenzoate (sometimes together with other factors), which is apparently a growth factor for these species of plasmodia. It has long been known that the course of infections can be modified by the diet of the host. According to a review by McKee (1951), the growth of various plasmodia has been reported at different times to be depressed by feeding the host on diets deficient in *p*-aminobenzoate, methionine, ascorbic acid, vitamin A, riboflavine, or pantothenate, but to be increased by diets deficient in biotin, folic acid, nicotinic acid, choline, or protein.

In particular, Geiman and McKee (1948) found that if monkeys were starved they were not susceptible to infection with *P. knowlesi*, but they became susceptible if given *p*-aminobenzoate or methionine. There is a striking parallelism between their experiment and the ones described above, in which monkeys were not susceptible to this infection when kept on a milk diet, but became susceptible if given *p*-aminobenzoate. Previously, workers of their group had shown that *p*-aminobenzoate was necessary for the growth of *P. knowlesi in vitro* (Anfinsen *et al.*, 1946).

Further evidence for the relation of this compound to the growth of malaria parasites is given by the sensitivity of many species of plasmodia to sulphonamides (which antagonize *p*-aminobenzoate). Thus *P. knowlesi* and *P. berghei* are very sensitive to sulphonamides (and their growth is prevented by a milk diet but promoted by *p*-aminobenzoate); *P. gallinaceum*, *P. cynomolgi*, *P. falciparum*, and *P. vivax* are moderately sensitive to sulphonamides (the growth of *P. cynomolgi* is inhibited by a milk diet, etc.); while *P. relictum* is insensitive to sulphonamides (its response to a *p*-aminobenzoate-free diet has not yet been elucidated). It may be noted, however, that the amount of *p*-aminobenzoate which has usually to be added to the milk diet of rats to promote the growth of *P. berghei*—namely, the equivalent of 20 mg. per kg. of rat per day—is much greater than the amount which is probably provided by the normal stock diet.

Relation to Proguanil and Pyrimethamine

The recognition that *p*-aminobenzoate is a growth factor for the malaria parasites helps to elucidate the antimalarial action of proguanil and pyrimethamine, since (1) under suitable conditions the antimalarial action of proguanil and pyrimethamine upon *P. berghei* can be antagonized by *p*-aminobenzoate (Thurston, 1950, 1954); therefore these drugs probably interfere with the utilization of *p*-aminobenzoate (or some derivative like folic acid); (2) there is often cross-resistance between proguanil and pyrimethamine on the one hand and sulphonamides (which antagonize *p*-aminobenzoate) on the other; (3) pyrimethamine inhibits the growth of *Lactobacillus casei* and of *Str. faecalis in vitro*, and this inhibition can be overcome by folic or folinic acid (Hitchings, 1952).

Functions of p-aminobenzoate

The need of many malaria parasites for *p*-aminobenzoate is of particular interest because so much work has been done by microbiologists in elucidating the role of this compound in cell metabolism. Attention was first drawn to it because it antagonized the antibacterial action of sulphonamides (Woods, 1940). The exact details of its action are still the subject of controversy; but, briefly, (1) much (but not all) of the *p*-aminobenzoate absorbed by bacterial cells is built up into pteroylglutamic acid (folic acid), folinic acid, or some similar compound; (2) *p*-aminobenzoate and/or a folic acid derivative acts as a catalyst in various important synthetic reactions, by which (usually) an extra carbon atom is added to some molecule such as an amino-acid; thus homocysteine is converted into methionine, glycine into serine, etc.; (3) *p*-aminobenzoate or its derivative is necessary as a catalyst for the synthesis of purine and pyrimidine rings (probably by the addition of another carbon atom); these are fundamental for the synthesis of nucleic acids and nucleoprotein, and so for the growth and multiplication of nuclei and cells.

In the case of the malaria parasite, morphological evidence for this relation between the supply of *p*-aminobenzoate and the division of the nucleus is provided by the following facts. The utilization of *p*-aminobenzoate by the parasite is antagonized by sulphonamides, proguanil, and pyrimethamine. If malaria parasites—for example, *P. falciparum*, *P. cynomolgi*, or *P. berghei*—are exposed *in vivo* to the action of one of these drugs the early development of the parasite inside the erythrocyte—that is, from ring to trophozoite—proceeds apparently unaffected. But when the chromatin (nucleus) begins to divide to form the schizont, morphological evidence of profound disturbance becomes manifest; division of the chromatin is arrested or takes place abnormally; and then the parasite gradually degenerates and disintegrates (Black, 1946; McFadzean, 1951; Thurston, 1951). Thus interference with the utilization of *p*-aminobenzoate prevents normal division of the nucleus (chromatin), perhaps because the synthesis of new nucleoprotein has been interrupted. The development of the gametocytes does not involve the need for so much new nucleoprotein, and it is not noticeably disturbed by sulphonamides and similar drugs. However, there is disturbance and suppression of the subsequent development of the gametes after conjugation—that is, the development of the oocyst—during which much nuclear division normally takes place.

Human Malaria

Finally, the application of this work to human malaria may be considered. It is said that there is a widespread belief in Arab countries that a milk diet protects against attack by malaria; on the supposition that this milk diet was not supplemented by other foods containing *p*-aminobenzoate, this belief would seem to possess biochemical justification. Further information of such folk-beliefs relating to milk and malaria would be welcome, even though such situations are of interest rather than of importance. Much more practical is the question of babies and malaria. It has long been recognized that babies in West Africa and similar hyperendemic regions do not contract malaria as early or as intensely as would have been expected from the degree of their exposure to infected mosquitoes (cf. Bruce-Chwatt, 1952; Reed, 1952). It has previously been considered that such early insusceptibility might be due to immunity inherited or acquired from the mother. In view of Maegraith's discovery and of the work reported above, it seems quite possible that their insusceptibility might rather be due to their milk diet—that is, their deficiency of *p*-aminobenzoate. The common human malaria parasites, *P. falciparum* and *P. vivax*, are suceptible to sulphonamides, and therefore they presumably require *p*-aminobenzoate as a growth factor.

Babies in Africa, and presumably most other parts of the Tropics, are at first fed exclusively on the breast; during this period, which may last for five or more months, they would theoretically be insusceptible to malaria. After this period their diet is supplemented with various pastes or porridges of ground grain, etc.; if these contain *p*-aminobenzoate (as will often be the case) the increased malaria rate in babies at this age group is easily explained. Some babies, however, do get malaria at 3 months or earlier, when it is improbable that their diet is supplemented by solid food. In such cases it is possible that the mother may have absorbed increased quantities of *p*-aminobenzoate (either from her own diet or from unusual bacterial synthesis in the intestine) and she may have passed it via the milk to the baby. All these hypotheses are well supported by the experiments with suckling rats and monkeys described above, but extensive and circumspect observation in the field will be required before they can be proved or disproved.

Summary

Rats fed on a milk diet are insusceptible (or only slightly susceptible) to infection with *Plasmodium berghei* (Maegraith, Deegan, and Jones, 1952). This insusceptibility can be reversed by the addition to the diet of *p*-aminobenzoate, which seems to be a growth factor for many species of malaria parasite. The insusceptibility can also be produced by maintaining rats on other diets deficient in *p*-aminobenzoate.

The addition to the milk diet of 20 mg. of *p*-aminobenzoate per kg. of body weight per day was sufficient to permit normal multiplication of the malaria parasite.

The deficiency in the milk could also be corrected by adding folic acid (in molar amounts corresponding to the amount of *p*-aminobenzoate needed), but not by adding methionine, vitamin B_{12}, or *p*-hydroxybenzoate.

Monkeys maintained on a milk diet were insusceptible to infection by *P. knowlesi* or *P. cynomolgi*, but they became fully susceptible when *p*-aminobenzoate was added to the milk in amounts of 0.5 mg. per kg. of body weight per day.

Baby rats and baby monkeys, while exclusively breast-fed from their mothers, are (almost or completely) insusceptible to infection with *P. berghei* or *P. cynomolgi* respectively, provided that their mothers are fed on a diet deficient in *p*-aminobenzoate. If this substance is administered either to them or to their mothers they become fully susceptible.

It is suggested that the relative immunity to malaria shown by infants under 6 months in many parts of the Tropics may be due to a deficiency of *p*-aminobenzoate in their diet of mother's milk.

Grateful acknowledgments are due to Dr. A. T. Fuller for the estimations of *p*-aminobenzoate by bioassay, and to Mr. K. Broomfield and Miss J. P. Selby for invaluable technical assistance throughout these experiments.

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CANCER OF THE TONGUE, MOUTH, AND PHARYNX

SEX DIFFERENCES IN PROGNOSIS FOLLOWING RADIOTHERAPY*

BY

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In the presentation of morbidity and mortality surveys of malignant disease in sites affecting both sexes it is customary for the sex incidence rates to be stated separately. This principle is rarely observed, however, in the presentation of treatment results. Omission of the sex factor, in a series of cases large enough to render separate analyses practicable, may well have the effect of concealing real differences in prognosis. The object of this survey is to demonstrate, by separate sex analysis of the comparative results of treatment of cancer of the tongue, mouth, and pharynx, that such results not only can exist but may be substantial.

It is shown that in females the overall treatment results are much higher, and that post-operative mortality, recurrence rate, and incidence of secondary lymph nodes are lower.

Basis of the Survey.—The data analysed are from 673 cases of cancer of the tongue treated by radium implantation, 916 cases of cancer of the mouth, and 550 cases of cancer of the pharynx—a total of 2,139 cases treated by radium or deep *x* rays at the Christie Hospital and Holt Radium Institute, Manchester, during the years 1932 to 1942 inclusive. Evaluation of differences in response has been conducted in relation to the state of affairs ten years after treatment.

Criteria of Classification

The primary sites conform to International List Nos. 141–6, with the exception of soft palate, which is excluded from the sites covered by No. 144, and fauces and tonsil, which are excluded from No. 145, for reasons which are explained later.

For the purpose of presenting the findings in concise form, subdivisions in tables have been kept to a minimum, although the data have actually been analysed first in greater detail to ensure that no bias would be introduced by this procedure.

Although this survey is not concerned with the evaluation of particular treatment methods, it is necessary to state—again in the interests of eliminating possible bias—that no sex discrimination was exercised in the application of particular techniques. For tongue cases radium implantation was used; for mouth and pharynx the techniques employed were (*a*) radium used by intracavitary, interstitial, or surface applicator method; (*b*) deep *x*-ray therapy. Where technically and physically practicable, cervical lymph node involvement was dealt with by block dissection: in a proportion of cases no form of treatment was deemed useful; in others, radiation was used as an alternative. No significant difference was found between the sexes in the proportions of the various techniques or between the four clinical stages of advancement.

The term "node-free" implies that in the cases so described there was no clinical evidence of cervical lymph node involvement at the time of treatment; the group represents summation of stages I and II according to the convention devised at the Christie Hospital and Holt Radium Institute, and, since its adoption elsewhere, known as the Manchester staging. Full details of the staging convention were given by Paterson, Tod, and Russell (1950). The term "nodes involved" indicates the presence of clinically palpable lymph nodes at the time of treatment, and represents summation of stages III and IV. Distant metastases rarely occurred, and almost invariably there already was cervical invasion. No useful purpose seemed to be served, therefore, by reporting them in this particular study.

*This paper, confined to cancer of the tongue, was read at the 7th International Congress of Radiology held in Copenhagen, July 19–25, 1953. Mouth and pharynx cases have since been investigated on similar lines, and the results are now embodied in the paper.

Statistical Method

In the tables relating to 10-year survival the description "age-corrected rate" means that the crude rate has been corrected by age as a factor in the assessment of treatment results, this rate having been calculated by application to the crude survival rate of a weighted probability designed to correct for deaths due to intercurrent causes with no evidence of residual or recurrent cancer at the time of death. If any realistic picture of 10-year results is to be obtained such a correction is essential. The crude survival rate is included for purposes of comparison, although it underevaluates the long-term effect of cancer treatment. A detailed account of the age factor method of correction was discussed and applied by Paterson *et al.*

Percentages are shown rounded off to the nearest whole digit. Statistical tests of significance have been applied to the results, and in commenting on the differences the following convention is adopted: the term "significant" is in general used when the observed differences exceed the conventional level of twice the standard deviation to a limit of 2.57. The probability of the difference in results being due to chance would thus range from 1 in 20 to 1 in 100. Where the differences meet even more stringent tests they are referred to as "highly significant." In some instances, where the distributions indicate the desirability of a different statistical method of evaluation, the same criterion of significance obtains.

Section I. Cancer of the Tongue and Mouth

Sex Differences in Distribution and Response

Table I gives the distribution in terms of sex incidence and primary site of the data for analysis. The sex ratio male to female on the total cases in tongue and buccal cavity respectively is almost identical, but there are marked differences between individual sites. It is noticeable, for example, that comparatively few women have lesions arising in the posterior third of the tongue. It is equally noticeable from the distribution of the anterior buccal cavity cases that, in men, lesions arising in the lower part of the mouth predominate, although this is not so in women. The word "incidence" in this context is, of course, used in the restricted sense of describing the relative frequency of the treated cases for investigation. Incidence rates and their changing pattern, based on a defined population, are the subject of a separate survey in course of preparation.

TABLE I.—*Data for Investigation*

Primary Site	Cases	Males	Females	Ratio Males to 1 Female
Tongue:				
Anterior two-thirds ..	522	422	100	4·2
Posterior one-third ..	151	138	13	10·6
Total ..	673	560	113	5·0
Buccal cavity:				
Floor	427	395	32	12·3
Cheek	215	160	55	2·9
Lower alveolus/gum ..	177	144	33	4·4
Upper „ „ ..	34	20	14	1·4
Hard palate	63	49	14	3·5
Total ..	916	768	148	5·2

Reference has already been made to the exclusion of the soft palate. Technically and aetiologically this site seems to be more suitably grouped with the posterior buccal cavity (or faucial) region. During the years under review 656 cases arising in fauces, tonsil, and soft palate were treated, distributed as follows:

	Males	Females	Ratio Males to 1 Female
Fauces	368	15	24·5
Soft palate ..	161	2	80·5
Tonsil	100	10	10·0
	629	27	23·3

These figures indicate the futility of investigating sex differences in prognosis in this particular region. When the hard-palate and soft-palate cases are grouped together—in the present instance giving a sex ratio male to female of 13.1 : 1—the great disparity in the ratios for hard and soft palate separately (3.5 : 1 and 80.5 : 1) is obscured.

This characteristic of very low incidence in women is, as is well known, also common to the lip—a site which is sometimes included in mouth surveys, but which again is rendered impracticable in this context by the paucity of female cases.

The age distribution by sex, expressed as a percentage, is shown in quinary groups in Fig. 1. In women the disease manifests itself at an earlier age than is the case in men. Thus, in the tongue cases the modal age group occurs a decade earlier, and in the mouth cases five years earlier. Reference is made later to the need for taking into account these disparities in age distribution.

In Table II the 10-year results for the two groups of cases are shown separately by sex. Crude survival and age-corrected rates reveal considerable differences between males and females. Although, as previously stated, age-corrected rates offer a better assessment of the efficacy of treatment, the differences between the crude survival rates are of much the same order and are highly significant.

If the overall survival rate is considered in relation to cervical lymph node involvement at the time of treatment of the primary lesion (Table III), the analysis is seen to yield the same trend of a higher rate in women, although, not unexpectedly, the differences in the later stages of the disease are not statistically significant. In the node-free group, however, the differences are highly significant.

It is pertinent to examine next the various factors contributing to the overall differences already demonstrated. The factors for investigation are: post-operative mortality; incidence of recurrence; incidence of cervical lymph nodes before treatment; subsequent cervical involvement.

Post-operative mortality is the first major hazard to be encountered after treatment. It is logical to deal with it first from a statistical point of view also, since its impact somewhat reduces the number of cases available for investigation of other phenomena. Table IV shows that, whereas the post-operative mortality rate for men with cancer of the tongue is 15%, the corresponding rate for women is only 4%—a difference which is highly significant. In the buccal cavity, where there is an apparently lower risk to men, the difference between male and female rates of 7% and 4% does not reach the conventional level of statistical significance, the probability of chance occurrence being 1 in 5. The fact that there is a heavier weighting of men in the higher age groups has already been shown. Nevertheless, the analyses in both tongue and buccal cavity groups reveal a male excess mortality in most age groups.

Having observed striking sex differences in the post-operative mortality rate, it is worth while to look at these

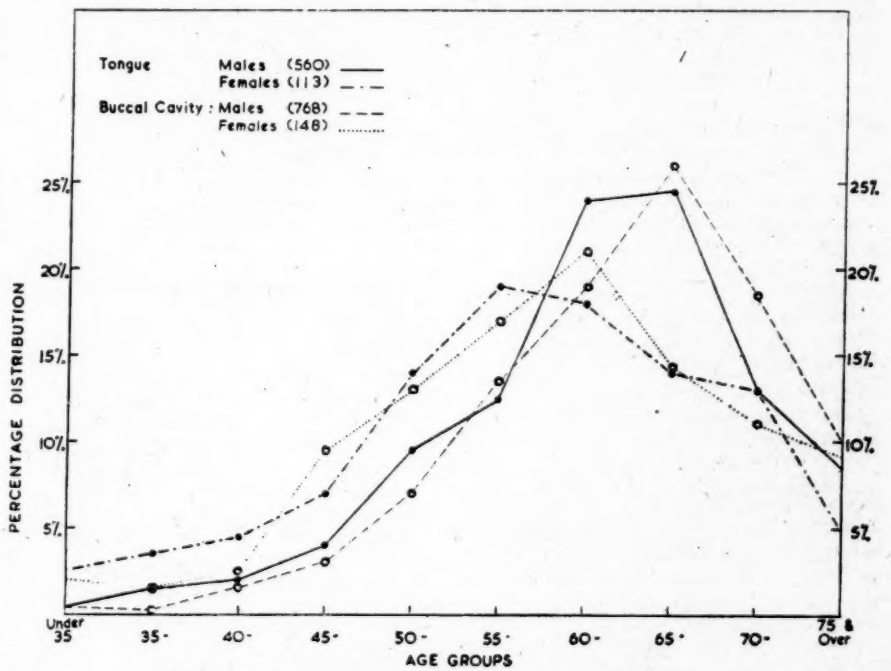

FIG. 1.—Age distribution of cases of cancer of the tongue and buccal cavity given radiotherapy during 1932–42.

TABLE II.—*Comparison by Sex of 10-Year Survival Rates*

Sex	Tongue			Buccal Cavity		
	No. Treated	Crude	Age-corrected	No. Treated	Crude	Age-corrected
Male ..	560	13%	23%	768	18%	32%
Female ..	113	31% (a)	42%	148	34% (b)	47%
Total ..	673	16%	26%	916	20%	32%

(a) P<0·0001. (b) P<0·0001.

TABLE III.—*Comparison by Sex and Clinical Findings of 10-Year Survival Rates*

Clinical Findings	Sex	Tongue			Buccal Cavity		
		No. Treated	Crude	Age-corrected	No. Treated	Crude	Age-corrected
Node-free	M	352	20%	35%	416	25%	46%
	F	85	38% (a)	51%	91	46% (b)	71%
Nodes involved	M	208	2%	4%	352	9%	16%
	F	28	11% (c)	13%	57	12% (d)	18%

(a) 0·0001<P<0·001. (b) P<0·0001. (c) P=0·08. (d) P=0·40.

TABLE IV.—*Comparison by Sex and Age of Post-operative Mortality*

Age Group	Tongue				Buccal Cavity			
	Males		Females		Males		Females	
	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate
Under 50 ..	38	0%	20	0%	44	7%	23	0%
50–59 ..	124	17%	37	0%	159	7%	44	5%
60–69 ..	273	16%	36	8%	347	6%	52	6%
70+ ..	125	17%	20	10%	218	10%	29	3%
Total ..	560	15% (a)	113	4% (a)	768	7% (b)	148	4% (b)

(a) 0·001<P<0·01. (b) P=0·20.

further in relation to the effects of lymph node involvement. The figures for node-free tongue cases show (Table V) a significant difference in the rates of 10% and 2%. Node-free mouth cases provide the only instance of an equal rate for men and women. This is apparently due to the combined effect of known cardiac disease and old age in two

TABLE V.—*Comparison by Sex and Clinical Findings of Post-operative Mortality*

Clinical Findings	Tongue				Buccal Cavity			
	Males		Females		Males		Females	
	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate
Node-free	352	10%(*a*)	85	2%(*a*)	416	4%	91	4%
Nodes involved ..	208	25%(*b*)	28	11%(*b*)	352	11%(*c*)	57	4%(*c*)

(*a*) $0.04 < P < 0.05$. (*b*) $P = 0.15$. (*c*) $P = 0.12$.

of the four deceased women in this group. Where lymphatic spread had occurred, appreciable differences exist between men and women in the respective rates of 25% and 11% for tongue and 11% and 4% for mouth, although they do not reach the significant level owing to the fact that the female groups are comparatively small. It should be borne in mind, of course, that these mortality rates were experienced in the years before antibiotics were in general use. Substantial reductions in post-operative mortality have been achieved since their introduction. Despite this beneficial effect, it is interesting to observe that an advantage still lies with females.

The next comparison to be made is the important one of recurrence rate of the primary lesion. This is evaluated more clearly by confining analysis to cases originally classified node-free. The term "recurrence rate" is a convenient one to use, but it has a wider application in this context than it has when used in relation to radical surgery. As the post-treatment phase for tumours treated *in situ* is one of regression at varying rates, apparent quiescence of a residual lesion or—in tumours of a completely radio-resistant character—steady advancement of the malignant process, recurrence rate actually implies apparent failure of the primary to resolve completely as well as recurrence after an interval of freedom from sign or symptom.

It has been necessary to deduct the post-operative deaths from this group, since these cases were no longer available for observation. In Table VI, which for tongue cases shows

TABLE VI.—*Comparison by Sex of Incidence of Primary Recurrence in Node-free Group (After Deduction of 98 Post-operative Mortality Cases)*

Sex	Tongue		Buccal Cavity	
	No. Observed	Primary Recurrence Rate	No. Observed	Primary Recurrence Rate
Male	318	41% } (*a*)	360	36% } (*b*)
Female	83	21% }	85	22% }

(*a*) $0.0001 < P < 0.001$. (*b*) $0.01 < P < 0.02$.

TABLE VII.—*Comparison by Sex of Incidence of Cervical Lymph Nodes Before Treatment*

Clinical Findings	Tongue		Buccal Cavity	
	Males	Females	Males	Females
Node-free ..	352	85	416	91
Nodes involved ..	208	28	352	57
Total ..	560	113	768	148
Proportion with nodes involved	37%	25%	46%	39%
	(*a*)		(*b*)	

(*a*) $0.01 < P < 0.02$. (*b*) $P = 0.10$.

a primary recurrence rate of 41% in men as opposed to 21% in women, a highly significant difference is demonstrated. The rates of 36% and 22% for mouth cases similarly disclose that recurrence is much less frequent in women than in men, the observed difference being significant.

Sex differences in cervical lymph node involvement at the time of original examination are shown in Table VII. In both tongue and mouth lesions a higher rate exists in males than in females: in the former group the difference is near to high significance; in the latter it is not significant at the conventional level, the probability of chance occurrence being 1 in 10. Nevertheless, these trends suggest the desirability of investigating the incidence of lymph nodes after treatment of the primary lesion in the group of cases originally classified as node-free.

The results of the analysis of the final factor investigated are shown in Table VIII. For tongue lesions the greater susceptibility of men to subsequent cervical involvement is

TABLE VIII.—*Comparison by Sex of Development of Cervical Lymph Nodes in Cases Originally Node-free (After Deduction of 98 Post-operative Mortality Cases)*

Sex	Tongue		Buccal Cavity	
	No. Observed	Lymph Node Incidence Rate	No. Observed	Lymph Node Incidence Rate
Male ..	318	60% } (*a*)	360	49% } (*b*)
Female ..	83	47% }	85	27% }

(*a*) $P \simeq 0.03$. (*b*) $0.0001 < P < 0.001$.

indicated by the male and female rates of 60% and 47% respectively, and is statistically significant. The same trend is disclosed in the mouth group, in which the difference between the rates of 49% and 27% is highly significant.

Section II. Cancer of the Pharynx

Difficulties implicit in dealing with cancer in this site are inevitably encountered in attempting to investigate sex differences in prognosis according to the pattern adopted in Section I. In a site of such unfavourable prognosis clinical and technical handicaps are unavoidably reflected in any statistical evaluation, and consequently less precision is attainable in the assessment of certain characteristics. The same trends of better prognosis in the female are nevertheless demonstrable, and seem to be worth recording in somewhat condensed form.

TABLE IX.—*Data for Investigation*

Primary Site	Cases	Males	Females	Ratio Males to 1 Female
Nasopharynx and oropharynx	287	208	79	2·6
Hypopharynx and post-cricoid	263	141	122	1·2
Total	550	349	201	1·7

Sex Differences in Distribution and Response

The data for analysis are divided into two broad groups, as shown in Table IX. In the nasopharynx and oropharynx the frequency ratio indicates much less disparity between the sexes than is the case for the tongue and mouth, and scarcely any for lesions arising in the hypopharynx and post-cricoid region.

Figure 2, giving the age/sex distributions, shows no difference in the modal age group for males and females in the nasopharynx and oropharynx. As there were more patients in the younger age groups than was the case in tongue and mouth lesions, the range of quinary age groups has been expanded. The distribution for hypopharynx and post-cricoid region shows a sharp rise to the modal age of 65–69 for males, the corresponding peak for females being 60–64.

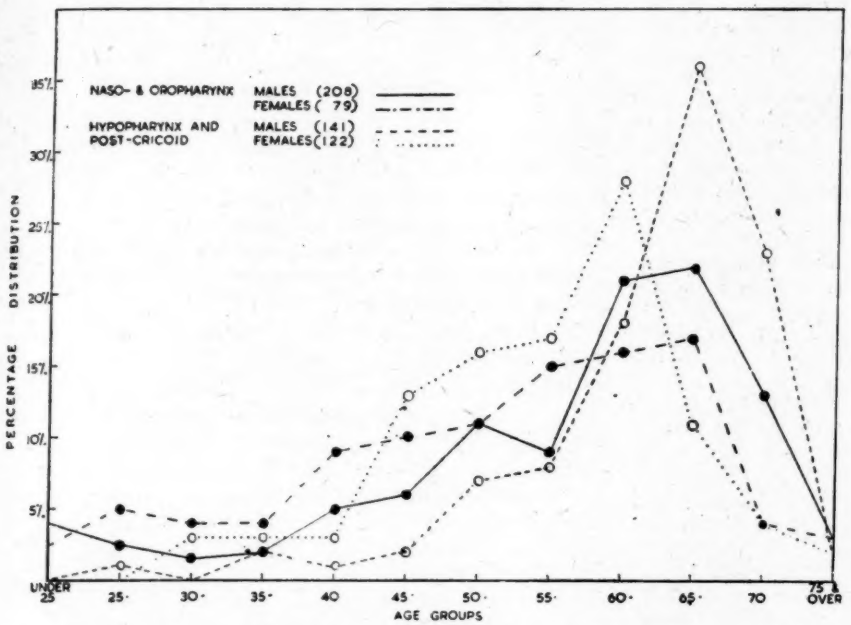

FIG. 2.—Age distribution of cases of cancer of the pharynx given radiotherapy during 1932–42.

Comparison by Sex of 10-Year Survival Rates

A highly significant difference between males and females is shown for the nasopharynx and oropharynx group (Table X). It may also be observed that the 10-year results for women are as good as the survival rates experienced by men with cancer of the tongue. On the other hand, the long-term results for hypopharynx and post-cricoid region cases reveal uniformly poor prognosis.

TABLE X.—*Comparison by Sex of 10-Year Survival Rates*

Sex	Naso- and Oropharynx			Hypopharynx and Post-cricoid		
	No. Treated	Crude	Age-corrected	No. Treated	Crude	Age-corrected
Male ..	208	6% } (a)	8%	141	3%	5%
Female ..	79	19% } (a)	23%	122	2%	3%
Total ..	287	9%	12%	263	3%	4%

(*a*) 0·0001 < P < 0·001.

TABLE XI.—*Comparison by Sex and Clinical Findings of 10-Year Survival Rates*

Clinical Findings	Sex	Naso- and Oropharynx			Hypopharynx and Post-cricoid		
		No. Treated	Crude	Age-corrected	No. Treated	Crude	Age-corrected
Node-free	M	28	7% } (a)	12%	39	5%	9%
	F	19	16% } (a)	21%	48	4%	6%
Nodes involved	M	180	6% } (b)	7%	102	2%	4%
	F	60	20% } (b)	24%	74	1%	2%

(*a*) P = 0·65. (*b*) 0·0001 < P < 0·001.

TABLE XII.—*Comparison by Sex and Age of Post-operative Mortality*

Age Group	Naso- and Oropharynx				Hypopharynx and Post-cricoid			
	Males		Females		Males		Females	
	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate
Under 50	44	9%	27	0%	8	13%	26	12%
50–59 ..	41	5%	21	5%	21	38%	41	17%
60–69 ..	90	23%	26	12%	76	21%	48	13%
70+ ..	33	15%	5	0%	36	17%	7	14%
Total ..	208	15%(a)	79	5%(a)	141	22%(b)	122	14%(b)

(*a*) 0·02 < P < 0·05. (*b*) P = 0·09.

Analysis according to the presence or absence of cervical lymph node involvement (Table XI) is not very profitable in view of the low numbers in the node-free group of nasopharynx and oropharynx cases and the poor results already seen in Table X for hypopharynx and post-cricoid region cases. Nevertheless, the trend in the former again shows an appreciably higher rate for women, which might well prove to be a significant one if more cases were available for study. Where cervical involvement had taken place the higher survival rate for women is highly significant.

Table XII reveals the overall post-operative mortality rates for cancer of the nasopharynx and oropharynx to be almost identical with those for cancer of the tongue, and significantly higher in males. Unlike the tongue and mouth cases, however, the heaviest rate for each sex occurred in the decade 60–69. The difference of 8% between the male and female rates for hypopharynx and post-cricoid, although not great enough to be statistically significant, follows the same trend.

Analysis of the cases according to cervical lymph node involvement also shows a similar trend throughout of a higher rate for men, but the consequent decrease in numbers in each group results in none of the differences being significant. No useful purpose seemed to be served, therefore, by the inclusion of a table in this form.

It is not practicable in this section to include a table dealing with recurrence of the primary lesion in node-free cases, as was done in Section I. Complications such as oedema and stenosis encountered in the hypopharynx and post-cricoid region result in any attempt at assessment being highly presumptive, even with an endoscopic examination and biopsy, and consequently undesirable as a basis of statistical evaluation. In the nasopharynx and oropharynx the same difficulties exist, but in a lesser degree. It seems probable here that 57% of men and 42% of women experienced recurrence in the primary site, but this assessment must be regarded as being less reliable than that quoted for the tongue and the mouth.

TABLE XIII.—*Comparison by Sex of Incidence of Cervical Lymph Nodes Before Treatment*

Clinical Findings	Naso- and Oropharynx		Hypopharynx and Post-cricoid	
	Males	Females	Males	Females
Node-free	28	19	39	48
Nodes involved	180	60	102	74
Total ..	208	79	141	122
Proportion with nodes involved	87% (a)	76% (a)	72% (b)	61% (b)

(*a*) P = 0·03. (*b*) 0·04 < P < 0·05.

Cervical lymph node involvement prior to treatment of the primary lesion, which is the subject of analysis in Table XIII, occurs in both sexes to a far greater extent when the primary is situated in the pharynx than is the case when it is in the tongue or mouth. In each pharyngeal subgroup the rate for males is shown to be significantly higher than that for females.

Assessment of the risk of cervical lymph node involvement developing after treatment of the primary lesion is, of course, influenced by the response to treatment of the latter.

Where the prognosis is poor, the opportunity for observation of various characteristics is correspondingly limited. Furthermore, the node-free groups are small (Table XIII). It suffices to say, therefore, that the respective rates of 22% for males and 16% for females in nasopharynx and oropharynx cases, and 24% for males and 13% for females in hypopharynx and post-cricoid cases, follow the same trend as was observed for cervical invasion before treatment. The fact that these rates are so much lower than the comparable ones shown for the tongue and mouth cases is attributable to the shorter average duration of life. In the event of any future development of more effective methods of controlling the primary lesion they could not be regarded as an authentic estimate of potential lymph node involvement.

Discussion

Summarizing the findings, then, it would seem that in the treatment of cancer of the tongue, mouth, and pharynx female patients may be expected to respond much better than males and to resist lymphatic spread more successfully. In none of the aspects investigated—namely, long-term survival, incidence of post-operative mortality, primary recurrence, secondary lymph nodes before and after treatment of the primary lesion—has any evidence against this thesis emerged.

The fact that such sex differences in prognosis are demonstrable makes it obvious that, in the presentation of the results of treatment, omission of the sex and age distribution may well affect the deductions to be made from survival rates. Failure to keep this in mind may conceivably be the cause of some misinterpretation, since, in making comparisons, a higher survival rate attributed to improved technique may be due merely to differences in the sex ratio in the sample.

Furthermore, the need for the incorporation of an age-factor correction cannot be too strongly emphasized, particularly in countries where there is a rapidly increasing proportion of old people in the population. The consequent rising proportion of deaths from intercurrent diseases invalidates the crude mortality rate for purposes of treatment evaluation.

Revelation of differences in behaviour inevitably arouses speculation regarding the causes. Three obvious lines of inquiry seemed to be: (*a*) the possible effect of oestrogen changes; (*b*) the comparative incidence of syphilis; and (*c*) the respective standards of oral hygiene. Analysis of the results on a pre- and post-menopausal basis failed to reveal any real difference. The cases in which a Wassermann test had been made were invalidated for statistical purposes by the policy of clinical selection. Investigation of dental sepsis could not be undertaken in a survey of retrospective character, but there is a strong suggestion from various sources that the standard of oral hygiene is appreciably higher in women than in men.

It may be that investigation of possible local influences would yield only a partial solution, and that the differences now demonstrated are merely a cogent example of the fact that the female, although lacking equal physical strength, is nevertheless fundamentally possessed of greater stamina than the male. In a comparison of male and female mortality trends, Martin (1951) showed that the disadvantage experienced by males has been increasingly enhanced during the past few decades. An analogy is to be found in various other species in which there is an excess mortality of males over females.

Despite the fascination of speculation, the initial function of the statistician is to indicate where such sex differences in prognosis exist, in the hope that medical research workers from other fields may be induced to explore some of the by-ways.

Summary

Three groups of cancer cases—673 in the tongue, 916 in the buccal cavity, and 550 in the pharynx—treated by radium or deep *x* rays at the Christie Hospital and Holt Radium Institute, Manchester, during the years 1932 to 1942 inclusive are analysed separately by sex ten years after treatment, for the purpose of demonstrating a marked difference in prognosis.

Survival rates are given in terms of the whole group irrespective of the degree of clinical involvement at the time of treatment, and also in relation to the presence or absence of extension of the disease to cervical lymph nodes. Relevant factors, including post-operative mortality, incidence of recurrence, and incidence of cervical lymph nodes before and after treatment of the primary lesions are investigated.

In all the directions explored the same trend emerges in support of the thesis that a much better response to treatment is manifest in women than in men. Women are also less prone to develop metastases. Some possible influences are considered.

The opinion is expressed that, in the presentation of the results of treatment of malignant disease, failure to state the sex and age distribution may result in fallacious deductions when comparisons are being made between different series of cases. Attention is also directed to the inadequacy of the crude survival rate for purposes of long-term evaluation, and the necessity for incorporating an age-factor correction is emphasized.

I am indebted to Dr. Ralston Paterson, from whose criticism of my original draft I derived much benefit; to Dr. Edith Paterson for helpful suggestions; to Professor Victor Lambert for useful advice: and to my assistants in the medical statistics department for their aid with the analyses, graphs, and typing of the paper. I wish to record, too, my appreciation of the encouragement and courageous interest of the late Dr. Margaret C. Tod during her terminal illness.

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CANCER OF UTERUS: RELATIVE INCIDENCE OF TYPES

BY

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Carcinomas of the uterus are commonly divided into three groups: (1) epidermoid carcinoma of the cervix; (2) adenocarcinoma of the cervix; and (3) endometrial carcinoma of the "body." The first and third groups together account for over 90% of uterine carcinomas.

Cases under Review

During the past four years 1,612 uterine specimens have been examined in this hospital. These were composed of endometrial curettings, 1,135; uteri, 286; and cervical biopsies, 191. During this period carcinoma of the body has been diagnosed in 34 cases, epidermoid carcinoma of the cervix in five cases, and adenocarcinoma of the cervix in one case.

The age distribution of the cases of adenocarcinoma of the endometrium is shown in the Table. The mean age

was 55 years. The marital status was 26 married and 9 single. The age distribution of the cases of epidermoid carcinoma of the cervix is also shown in the Table. The mean age was 45 years. Three were married and two were single.

Age Distribution of 34 Cases of Adenocarcinoma of the Endometrium and Five Cases of Epidermoid Carcinoma of the Cervix

	31–	36–	41–	46–	51–	56–	61–	66–	71–	76–80
Adeno-carcinoma		3	2	3	13	4	3	3	2	1
Epidermoid carcinoma	1		2		1	1				

The relative incidence of cases of carcinoma of the body and the cervix is 7 : 1. This ratio is so different from the textbook figures that the following points must be noted.

Firstly, the patients are drawn from a selected portion of the community, as this hospital deals almost entirely with the upper- and middle-income groups of Cork City and surrounding country. Secondly, the cases considered to be carcinoma of the endometrium are only those showing frank histological evidence of carcinomatous change; any case showing only atypical hyperplasia was excluded. The fact that the cases were collected over a period of four years would seem to exclude any chance selection in a short period. It would also exclude, to a large extent, the possibility of a number of cases of carcinoma of the cervix having been "missed." To bring the figures to accepted proportions over a hundred cases of cervical carcinoma would have had to escape notice, and, so far as we are aware, no patient in this series who was not diagnosed as carcinoma of the cervix has returned with this condition. Lastly, the age distribution and mean age of both groups are typical. It would thus seem reasonably certain that in this series there is an actual and well-marked reversal of the usually accepted frequency of carcinoma of the body and of the cervix.

To determine whether the atypical distribution was due to an increase in the number of cases of endometrial carcinoma or to a decrease in cases of cervical carcinoma a comparison was made with the figures of the Dublin maternity hospitals (*Irish Journal of Medical Science*, 1949, 1950, 1951). The incidence of endometrial carcinoma occurring per hundred operative gynaecological cases in the Dublin maternity hospitals was compared with that occurring in this hospital, and was found to be very similar. This fact indicates that the variation in our figures is due to an absolute decrease in the number of cases of epidermoid carcinoma of the cervix.

The Dublin reports also show that their relative incidence of the two types of uterine carcinoma is that generally accepted—that is, a preponderance of cervical carcinoma.

Discussion

Figures quoted for the relative incidence of the different types of uterine carcinoma vary, "but broadly it may be said that cervical carcinoma is three or four times as common as endometrial, and that cervical epidermoid carcinoma is at least ten times as common as cervical adenocarcinoma" (Willis, 1948). Novak (1952) gives the proportion as one endometrial carcinoma to eight cervical carcinomas.

It is becoming generally acknowledged that uterine carcinoma has socio-economic and racial distinctions. Stock (1947) has shown uterine carcinoma to be more common among the lower social class in England. He does not, however, distinguish between carcinoma of the endometrium and cervix. Clemmesen and Nielsen (1951) bring evidence to show that cervical carcinoma is more common in the lower socio-economic group, and that its incidence in rural areas approximates to the wealthier areas in the towns. The opinion that cervical carcinoma is more frequent in the lower-income group is also expressed by Lombard and Potter (1950). They state that "in a sample obtained from a gynaecologist who permitted a study of the records of his wealthy patients . . . the sample was small . . . owing to the fact that only a very small percentage of his private patients had carcinoma of the cervix." Again, Hall *et al.* (1950) found that, while the usual accepted relative incidence of the types of uterine cancer was valid for ward cases, in their private patients endometrial carcinoma was more frequent in the ratio 2 : 1. Corscaden and Gusberg (1947) also noted that in the private-patient group carcinoma of the endometrium was more common than carcinoma of the cervix.

While showing a much higher proportion than in any of the series quoted, our figures do agree in demonstrating that the usually accepted relative incidence of carcinoma of the endometrium to the cervix does not hold good for all sections of the community. They can also be used to show that in the socio-economic group concerned the disproportion observed is due to an absolute decrease in cases of cervical carcinoma rather than to an increase in endometrial carcinoma.

From the findings of the authors quoted and from our admittedly small group of cases it seems that one definite fact arises—that cancer of the cervix is more common in the lower socio-economic group. Our figures can do little more than suggest that the incidence of endometrial carcinoma may be much the same in all groups.

The reason for this low incidence of cervical carcinoma is obscure. Lombard and Potter (1950) list five factors which they claim have definite significance in the development of cervical carcinoma: marriage before the age of 20 years, unrepaired lacerations, last child born to women before the age of 25 years, syphilis, and individuals divorced or separated at any time. We considered these factors in relation to the class of patient dealt with in this hospital, and it was found, from a sample of married women, that the average age of marriage was 27 years; thus two factors —marriage before the age of 20 years and the last child born before 25 years—do not apply. Divorce and separation are exceptionally rare, as is syphilis. Of all these factors it is only unrepaired laceration of the cervix which might operate.

The relationship of cervical lacerations to cervical carcinoma is still undecided. An interesting contribution in this field is that of Gagnon (1950). This author investigated the medical histories of a large number of nuns, "women whose social state and mode of life protect them from the usual causes of cervicitis or chronic irritative lesions." He found that the ratio of endometrial carcinoma to that of cervical cancer was 6 : 1, and uses this fact among others to indite cervical lacerations as a factor in cervical carcinoma. In the discussion following this paper, McKelvey objected that the recognized low incidence of cervical carcinoma in the Jewish race still remained to be explained. Weiner *et al.* (1951) indicated that cervical carcinoma in Jewish women is becoming more common, and suggest that the Mosaic laws, which would tend to lessen the incidence of chronic cervicitis, are not now observed as rigidly as formerly. They, however, quote Davidsohn as believing that the difference in incidence of cervical carcinoma may be due to the practice of circumcision, a theory which is supported by the demonstration of the carcinogenic action of smegma.

Ovarian oestrogens have been suspected as a factor in carcinogenesis, and genuine carcinoma of the cervix has been produced in mice by Gardener, Li, and others (Novak, 1951). Ayre (1947) suggests that cervical carcinoma may be due to an abnormal response to cervical infection associated with excessive oestrogen, the latter being due to failure of a liver damaged by vitamin deficiency to inactivate oestrogen. Of interest in this connexion is the fact that Brunelli (1935) showed that in rabbits oestrogen in the blood becomes concentrated and fixed in inflamed tissues. Ayre's suggestions are criticized by Greene and Peckham (1947),

who point out that the previously accepted fact that vitamin-B deficiency, as such, decreases the inactivation of oestrogens by the liver has been shown to be untenable. Drill and Pfeiffer (1946) have shown that "the effect of acute vitamin-B-complex deficiency in producing a failure of the liver to inactivate oestrone seems to be due to the concomitant inanition."

If we may assume that cervical carcinoma is comparatively infrequent in the better-nourished members of a community, then there must be some factor or factors which lessen its occurrence in this group. Alternatively, in the undernourished group there must be some factor or factors which tend to cause this lesion. As cancer is an active condition it would seem more logical to suppose that poor economic conditions in some way produce this disease. Our present knowledge would suggest that cervical carcinoma may be produced in the poorer economic class by some unknown hormonal imbalance or by an unsatisfactory reaction, associated with poverty, to irritative lesions of the cervix.

Summary

Figures are given for the relative incidence of endometrial and cervical carcinoma as seen in a selected population.

These figures are at variance with the incidence usually accepted, and it is suggested that the incidence of the various forms of uterine cancer vary with the socio-economic group.

The possible implications of these findings are briefly discussed.

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The National Research Development Corporation exists primarily to develop and exploit in the public interest inventions (including medical ones) resulting from public research. It also has other powers. In June this year the Corporation's borrowing powers come to an end, and if the Corporation is to continue its normal activities new legislation will be necessary. The chance is therefore taken in the annual report for 1952–3, published recently, to review the results of the Corporation's first four years of trading. Starting in 1950 with costs of a little over £20,000 and a return by way of royalties of less than 1%, by 1953 the accounts showed 23% earnings on operating costs of £120,000. Several of the inventions being developed by the Corporation have a direct bearing on medicine. The pilot scale production of hecogenin from sisal juice in East Africa provides a starting material for the synthesis of cortisone. Prototypes of the Burns analgesic inhaler, designed for trilene and other volatile analgesics, have been prepared for clinical trial. The Corporation has underwritten the costs of the initial manufacture of an aural microscope and chick sexer. Other projects range from large electronic digital computers ("electronic brains") to a new machine for liquefying atmospheric gases.

DIABETES INSIPIDUS ASSOCIATED WITH PULMONARY DISEASE

BY

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Spillane (1952) described four cases in which diabetes insipidus was associated with pulmonary disease. The case here reported falls into the same category and exhibits diabetes insipidus and lung lesions as the only discoverable abnormalities.

Case Report

A housewife aged 57 was first seen in January, 1952, having been referred for further investigation after attending a mass *x*-ray session. She had suffered from increasing dyspnoea on exertion for about four years, with morning cough and the expectoration of a small amount of yellowish sputum. For several years she had passed large amounts of pale urine at frequent intervals during the day and night. She was also troubled by excessive thirst and said that she could drink a pint of soda-water at a time and still be thirsty. Her sleep rhythm was unchanged and there was no somnolence by day.

Before her present illness she had been healthy and had when younger often cycled 50 miles (80 km.) a day without distress. Until seven years previously she had worked as a waitress in addition to looking after her home, but she had had to discontinue this in order to look after her husband, who was becoming severely disabled owing to post-encephalitic Parkinsonism. She had had pneumonia on three occasions, at the ages of 23, 29, and 37; erysipelas at 14; and scarlet fever in childhood. There was no history of skin disease.

She was the second oldest of a family of 13 of whom five of six brothers had died in infancy, the other being killed in adult life. Of her six sisters, five were healthy and one had died 48 years previously, the cause of death being unknown. The patient had had two children, both of whom were healthy; her son was 34 and her daughter 28.

Examination revealed a rather pale middle-aged woman, weighing 134 lb. (60.8 kg.), an excellent witness, though inclined to make light of her complaints. Her skin was somewhat dry and wrinkled but otherwise showed no abnormality. No lymphatic glands were palpable and there was no enlargement of the salivary glands. Venous congestion, ankle oedema, and finger-clubbing were not present. She was somewhat dyspnoeic at rest, but no other clinical abnormalities were detected in the chest or heart. The blood pressure was 150/100. The abdomen showed no abnormality and the liver and spleen were not palpable. The optic disks were normal and neurological examination was negative.

Further investigation showed that she passed 12 to 16 pints (6.8 to 9.1 litres) of urine daily and drank roughly equal amounts. The specific gravity of the urine was in the neighbourhood of 1005; there was no glycosuria or albuminuria and no casts were present. *X*-ray films of the chest showed a mixture of reticulation and miliary mottling throughout both lung fields without enlargement of the hilar lymph nodes. No cysts were detected and there was no pneumothorax. *X*-ray films of the hands, feet, and skull showed no bony abnormalities. The pituitary fossa was radiologically normal.

Sputum tests for tubercle bacilli were repeatedly negative. The Mantoux test was positive to 1:1,000 O.T. Blood examination showed: Hb, 66% (9.8 g.%); erythrocytes, 5,000,000. The E.S.R. was 12 mm. in the first hour (Wintrobe). The blood Wassermann and Kahn reactions were negative and the glucose-tolerance curve was normal. The

serum cholesterol was 305 mg. per 100 ml.; serum albumin 5 g. and globulin 3.5 g. per 100 ml.; albumin/globulin ratio 1.43:1. Liver-function tests showed serum colloidal gold reaction 3+, gamma globulin (zinc sulphate) 8 units, thymol turbidity 4 units, and thymol flocculation +.

Pituitary snuff immediately controlled her polyuria and allowed her to sleep well at nights. After starting this treatment, however, she stated that her breathlessness was somewhat increased. Because of the hypochromic anaemia she was given iron, which resulted in some amelioration of the dyspnoea.

A year later her condition was unaltered and a further *x*-ray film of the chest showed no substantial change.

Comment

The diagnosis of diabetes insipidus cannot be in doubt, there being adequate evidence to exclude other causes of polydipsia and polyuria—that is, diabetes mellitus, renal disease, and hysterical polydipsia. The only other discoverable lesions were those in the lung, manifested by exertional dyspnoea and radiographic changes.

Spillane (1952) summarized fully the literature relating to this combination of lesions. Following him the diagnoses to be considered are sarcoidosis, tuberculosis, xanthomatosis, tuberous sclerosis, syphilis, honeycomb lungs, and bronchogenic carcinoma.

The first of Spillane's four cases was an undoubted example of sarcoidosis, and this diagnosis could not be excluded in his Case 4. The other two cases were considered clinically to be examples of xanthomatosis. Necropsy in Case 3 later showed, in the hypothalamus and the lungs, the changes of eosinophilic granuloma which shares a morphogenesis in common with Hand–Schüller–Christian and Letterer–Siwe diseases, all three being secondary xanthomatoses associated with progressive reticular hyperplasia. It is therefore interesting to note that one of Cates and Garrod's (1951) cases of diabetes insipidus occurred in a patient with xanthomatosis and honeycomb lungs who also developed an eosinophilic granuloma of bone.

Dennis and Rosahn (1951) reported the case of a man aged 30 with diabetes insipidus and cystic lungs. They concluded from the necropsy findings that it represented a granulomatous disease involving the reticulo-endothelial system.

In the present case sarcoidosis does not appear to be the most likely diagnosis. Spillane (1952) collected from the literature 18 cases of sarcoidosis associated with diabetes insipidus. In none were the lesions confined to the pituitary region and the lungs. Similarly his own Case 1, which was an example of sarcoidosis, had an initial characteristic uveo-parotitis with facial palsy. His Case 4, in which no certain diagnosis was reached, and in which sarcoidosis could not be excluded, showed lesions in these two situations only. In this respect it is similar to the present case in which the Mantoux test (positive to 1:1,000 O.T.) is rather against the diagnosis of sarcoidosis. In addition, the dyspnoea was more intense than might be expected in a case of sarcoidosis with similar radiographical findings.

If we adopt a histological definition of sarcoidosis, as does Scadding (1950), diagnosis must await confirmation by biopsy. In the present case no superficial glands were available for biopsy and, owing to her commitments at home, the patient was unwilling to accept admission to hospital for liver biopsy.

Although, therefore, it is not possible definitely to exclude sarcoidosis, a granulomatous or xanthomatous process seems by exclusion to be a more likely diagnosis.

It is possible that when lung changes and diabetes insipidus occur together as the only discoverable disease they constitute a syndrome the pathological basis of which is a granuloma of some as yet undetermined and possibly variable type. The two conditions may, however, occur as a part of more widespread pathological processes such as those indicated in the papers cited.

Summary

The case is described of a woman aged 57 who had diabetes insipidus associated with a combination of reticulation and miliary mottling throughout both lung fields. A granulomatous or xanthomatous process is thought to be the most likely diagnosis, though sarcoidosis cannot be definitely excluded.

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PULMONARY ACARIASIS IN SPAIN

AN ILLUSTRATIVE CASE REPORT

BY

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Considerable interest has been created in many parts of the world by the association that has been postulated by workers in Ceylon between hypereosinophilic respiratory disorders and pulmonary acariasis. Carter Wedd, and D'Abrera (1944) were the first to detect mites (Acarina) in the sputum of asthmatic patients with high eosinophilia. This discovery was confirmed by Soysa and Jayawardena (1945), who also suspected that the syndrome might result after exposure to inhalation of airborne mites. Further investigations in Ceylon by Carter and D'Abrera (1946) and by Soysa (1949, 1952a) have verified the previous findings. The conclusions of the Ceylonese workers that pulmonary acariasis may be associated with respiratory symptoms and massive eosinophilic reaction have been supported by reports from England (Hall, 1946), the Netherlands West Indies (Van der Saar, 1946), East Africa (Wilson, 1947), etc.

Since 1946 my attention has been engaged by the occurrence of mites in the sputum of certain patients with respiratory disorders associated with eosinophilic leucocytosis, and cases have been reported in Spain (Figueroa Taboada, 1946). I have been able, in my studies of this curious syndrome, to verify the ideas that have been so carefully and clearly presented by Soysa, and the results of my investigations are in complete agreement with his views concerning the three-stage clinical course discernible in many cases; the remarkable eosinophilic leucocytosis that is the most prominent and constant pathological feature of this syndrome; the variability of the pulmonary radiological appearances; the presence of mites in the sputum; the possibility of bronchial infestation by airborne mites; the ambient air importance of environment in relation to the acquisition of the disease; and the dramatic response to arsenical therapy, which is often associated with a Herxheimer reaction.

As an example of our findings in Madrid I cite a typical case history.

Case Report

A male clerk in a food store, aged 39, was investigated for asthma of seven months' duration. His personal and family history revealed no indication of any allergic antecedents. A blood count showed a total leucocyte count of

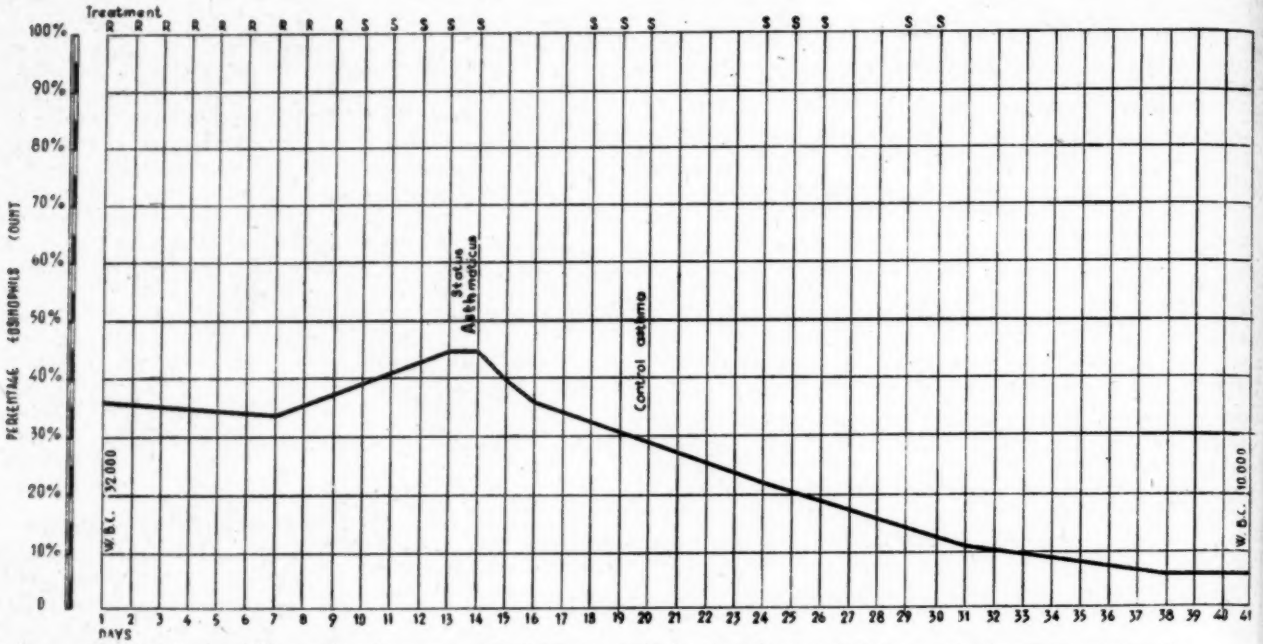

FIG. 1.—Eosinophilic reaction in a case of pulmonary acariasis. R=Routine treatment. S=Acetarsol treatment.

32,000 per c.mm., with 36% eosinophils. *X*-ray examination of the lungs showed fine linear striations superimposed upon the pathognomonic "ground-glass haze." Examination of the sputum by the special technique of Carter *et al.* revealed the presence of *Carpoglyphus* mites (Fig. 2).

FIG. 2.—Carpoglyphus.

Routine antispasmodic therapy for nine days produced no clinical response, while the eosinophils rose slightly. Acetarsol therapy was initiated thereafter, one tablet being administered twice daily for periods of five, three, three, and two days, separated by intervals of three, three, and two days, when the drug was suspended in order to prevent cumulative effects. The patient developed status asthmaticus on the fourth and fifth days of arsenical treatment. Clinical control of the asthma was affected by the tenth day. The leucocytes gradually declined to 12,500, with eosinophils 11% on the twenty-second day, and to 10,000, with eosinophils 6%, on the thirtieth day after starting acetarsol therapy (Fig. 1). The patient has had no recurrence of asthma for fourteen months.

Comment

This case conforms in all its features to the typical cases recorded by Soysa and confirms his observations as regards the symptomatology, pathogeny, and therapy of this syndrome. I believe that pulmonary acariasis is a perfectly delimited pathological entity which should be separated from allied respiratory disorders.

Though generally regarded as a tropical disease, this syndrome may be much commoner than it may seem to be in temperate zones, such as Europe, where the causal Acarina are widely distributed—for instance, in stored food products. In England have been found the mites of the genera *Carpoglyphus, Glyciphagus, Cheyletus, Tarsonemus,* and *Tyroglyphus* (Hughes, 1948). It seems possible, therefore, that careful examination of sputum in cases of eosinophilic respiratory disorders may disclose the presence of mites in countries that are not circumscribed within the tropical zone.

The laboratory procedure required for this purpose is long and laborious. Strict precautions have to be taken against accidental contamination of the specimens of sputum that have to be collected over a 24-hour period. The mass of material to be examined is so large that the work demands much patience and perseverance. The relatively small number of mites found in this quantity of sputum may appear insignificant, but it should be remembered that a few mites can cause disproportionate clinical disturbances in other acarine infestations, such as scabies. It may be argued that airborne mites may be prevalent in the respiratory passages without causing clinical or haematological manifestations. This objection has been met by the careful examinations made by Soysa (1949) of 44 control specimens of sputum taken from healthy persons and from patients suffering from non-eosinophilic respiratory diseases: not a single mite was found in any case, though 17 of these subjects were definitely exposed to the risk of inhaling airborne mites.

In a recent review of the aetiology and pathogeny of eosinophilic pneumonitis Soysa (1952b) discussed the various conditions that may present with somewhat similar clinical manifestations, and has suggested that, of the pathogenic agents that have been alleged to be responsible for eosinophilic pneumonitis, mites, metazoa, and fungi seem to come most under suspicion at the present time. He holds with the view that, despite the multiple aetiology and diverse pathological conditions that have been observed or suspected, the manifestations are linked by a common anaphylactoid pathogeny which is probably related to vascular allergy.

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TRICHLORETHYLENE POISONING WITH PARANOID PSYCHOSIS AND LILLIPUTIAN HALLUCINATION

BY

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There are few published reports of psychosis resulting from poisoning with trichlorethylene ("trilene"). Eichert (1936) recorded two cases and Rickles (1945) one case. All three arose from the excessive use of trichlorethylene inhalations to assuage the pain of tic douloureux. The opportunity to study the effects of orally ingested trichlorethylene has rarely arisen. However, Stephens (1945), Naish (1945), and Kallenback (1947) have between them described the toxic manifestations of swallowed trichlorethylene in four cases. In general, the symptoms consisted of prolonged inebriation, with vomiting, dizziness, deafness, or numbness of the limbs. The following case has some unique features.

Case Report

An Irish labourer aged 40 was admitted to Littlemore Mental Hospital on April 11, 1953. On April 5 he had accidentally swallowed a quantity of trichlorethylene contained in a beer bottle. The precise quantity ingested could not be ascertained, but was described as a "good swig." Realizing his mistake, he succeeded in vomiting up some of the liquid by swallowing an emetic mixture of salt and water. Nevertheless, his breath reeked of trichlorethylene and he was grossly inebriated on arrival at the casualty department of the Radcliffe Infirmary less than an hour after the accident. Despite stomach washouts (and other treatment), he passed into a deep coma lasting 36 hours. At times he was frankly cyanosed. The pupils varied in size from pin-point to wide dilatation with brisk light reaction. The B.P. varied between 90/50 and 140/70. On April 8, consciousness having returned the previous day, he developed a system of paranoidal ideas to the effect that he was going to be "beaten up" during the night by two patients in league with the nursing staff. That night he awoke in a state of delirium which he described as follows :

"The next thing I remembered was awakening to find myself soaked in sweat and strapped in a kind of long leather sack. I could hear the two patients who had spied on me during the day talking with the night nurses. One of them said, 'Let's give it to him now.' I opened my eyes, struggled free from the sack, and shouted for help. I then saw that the ward was its usual length, but only about 2 ft. high; the beds were about 18 in. long. In response to my cries a little nurse, 12 in. high, ran to my bed. I told her I was afraid, so she tried to reassure me, and went away to get a hot drink. While she was away, other nurses came to my bedside and were later followed by a doctor. They were all about 12 in. tall. I recognized all of them as the nurses and doctor I had seen before. The only other person besides myself who seemed the normal size was a patient in the bed next to mine. I thought he was a negro who was also being persecuted, but later found that he was white. I felt terribly afraid while all this was going on. They changed my shirt and gave me an injection. The next morning everything was back to its usual size."

During the next few days he continued to show evidence of a paranoid psychosis. For example, he complained that people were saying he had V.D., and that a nurse had "framed" him with a 10s. note introduced into his locker. His transfer to a mental hospital became necessary as a result of marked restlessness.

He was examined on his arrival at Littlemore Mental Hospital, with the following results. *Psychiatric condition:* During the first 48 hours he was unduly loquacious and lacking in insight. He still harboured delusions of a persecutory nature. The family and personal psychiatric histories were negative. *Physical condition:* He showed no physical abnormality with the exception of a coarse tremor of his extended fingers and a few persistent sibili at both lung bases. He was discharged in excellent mental and physical condition on April 25.

Special Investigations at Radcliffe Infirmary.—April 5: Hb, 100%; white cells, 20,000 per c.mm.; a neutrophil leucocytosis was present. April 8: Normal plasma proteins. No abnormal constituents of any kind in the urine.

Special Investigations at Littlemore Mental Hospital.—April 15: Blood urea, 30 mg. per 100 ml.; blood bilirubin, 0.2 mg. per 100 ml.; prothrombin level, 100%; plasma proteins, 7.1 g. per 100 ml.; urine testing showed no abnormal constituents. April 16: Hb, 115%; white cells, 10,000 per c.mm. April 20: Blood urea, 27 mg. per 100 ml.; blood bilirubin, 0.3 mg. per 100 ml.; prothrombin level, 100%; plasma proteins, 6.5 g. per 100 ml.; the urine contained no abnormal constituents.

Discussion

A noteworthy feature of this case is the fact that at no time was there any evidence of hepato-renal damage, despite the ingestion of enough trichlorethylene to produce a coma lasting 36 hours. This demonstrates a highly selective action of the substance on the central nervous system. Hunter (1949) showed that trichlorethylene has no serious toxic effect on the kidneys or liver of healthy mice. Ostlere (1953), after reviewing the literature, arrived at the conclusion that "the evidence of animal experiments, industrial toxicology, laboratory tests, and clinical practice clearly indicates that the toxic effects of trichlorethylene on the liver are negligible." The sparing of the liver cells by trichlorethylene is surprising, as the chemically related chloroform, carbon tetrachloride, and tetrachlorethane are notorious hepatotoxins.

The adjective "Lilliputian" was first used by Leroy (1909) to describe a rare form of visual hallucination consisting in the perception of imaginary objects, persons, or animals of diminutive size. These tiny animals or personages are usually seen as brightly coloured mobile creatures strongly reminiscent of those described by Swift in *Gulliver's Travels*. The perception of these colourful midgets tends to produce in the subject an agreeable emotional reaction, whereas the more usual forms of visual hallucination often engender a feeling of terror. The real environment does not usually participate in the Lilliputian contraction. In the case described, the microptic hallucinations took an exceptional (if not unique) form in that they represented real personages, were not coloured, produced a feeling of fear in the patient, and the ward was involved in the Lilliputian effect. In his delirium, the patient would appear to have experienced microptic *illusion* in addition to hallucination. Lilliputian hallucinosis has been described as a result of intoxication from alcohol, chloral, ether, cholera, and typhoid (Leroy and Rogues de Fursac, 1920). It has also been reported in the course of scarlet fever (Hall, 1922) and cocainism (Henderson and Gillespie, 1927). It is tempting to wonder if Dean Swift (or one of his friends) experienced the phenomenon at some time or another.

Summary

A case of accidental poisoning with trichlorethylene is described. An acute paranoid psychosis with Lilliputian hallucination followed a 36-hours coma. There was no evidence of hepato-renal damage at any time. In this case the microptic hallucination differed in many ways from the classical descriptions in the French literature.

My thanks are due to Dr. R. W. Armstrong, physician-superintendent of Littlemore Mental Hospital, Mr. W. A. McDougall, laboratory technician, and to the doctors of the Radcliffe

Infirmary. I am grateful to the medical and technical staff of Imperial Chemical Industries, who took a great interest in the case and analysed the parent liquid from which the beer-bottle sample was derived.

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Medical Memorandum

Traumatic Retroperitoneal Rupture of Duodenum

In view of the rarity of traumatic retroperitoneal rupture of the duodenum the following case is worthy of record.

CASE REPORT

A window-cleaner aged 17 was admitted on October 16, 1951, at 4.30 p.m. with a history of having fallen from a window-sill, a height of 20 ft. (6 metres), one hour previously. No one had seen him fall and he had been picked up by his workmate a few minutes later. He was quite conscious, but had no memory of falling. He was complaining of severe pain in his abdomen and was bleeding from his nose.

On examination his temperature was 98° F. (36.7° C.), pulse 92, respirations 20, and blood pressure 110/70. He was bleeding from both nostrils and he had a 1-in. (2.5-cm.) laceration of the chin. There was no obvious fracture of the nose or mandible. He complained of severe abdominal pain, mostly in the umbilical and hypogastric regions. He vomited twice during examination, and blood-staining of the vomitus was noticed, but the possibility of blood swallowed from his epistaxis was considered. Abdominal examination revealed abrasions and some bruising in the right iliac fossa. He was very tender, with some guarding over the whole abdomen, especially in the left iliac fossa. There was no rigidity. Bowel sounds were not heard. Dullness was not elicited in the flanks, and rectal examination caused no undue discomfort. A soft rubber catheter was passed to exclude bladder injury. It passed easily and 6 oz. (170 ml.) of clear urine was obtained. A diagnosis of ruptured abdominal viscus was made, and laparotomy was performed by one of us (W. P. C.) two hours after admission.

Operation.—Under thiopentone, cyclopropane, curare, and oxygen anaesthesia the abdomen was opened through a long right paramedian incision. A small quantity of free blood was present in the peritoneal cavity. By palpation no tear was found in either spleen or liver. Further inspection revealed a large left-sided retroperitoneal haematoma behind the descending colon and extending forwards between the layers of the pelvic mesocolon. The haematoma extended upwards and towards the right, and was continuous with a haematoma behind the hepatic flexure and the duodenum. The right kidney felt normal. Blood and extensive bile-staining were present in the lesser omentum. A laceration of the biliary tract was considered. The gall-bladder was normal and contained bile. The lesser omentum was incised and no lesion was seen in the common bile duct. Bile-stained fluid was coming upwards from behind the first part of the duodenum. The peritoneum along the right border of the duodenum was divided and the duodenum mobilized to the left. A 1-in. (2.5-cm.) linear tear was found on the posterior wall of the first part of the duodenum across the long axis of the bowel. Bile-stained contents were emerging. The tear was closed with two layers of continuous catgut. Examination of the whole bowel revealed no further lesion. Abdominal toilet was performed and the abdomen closed in layers with a stab drain to the duodenum. Extraperitoneal drainage of the left-sided retroperitoneal haematoma was carried out.

After operation 2 pints (1.1 litres) of blood was given by intravenous drip followed by alternating normal saline and 2½% dextrose. Gastric suction was instituted.

His progress was stormy. On the fourth post-operative day the stab drain to the duodenum discharged bile-stained fluid which digested the surrounding skin. Although not analysed, this was doubtless due to associated pancreatic trauma. It cleared up on the ninth day. The abdomen gradually distended and there were signs of paralytic ileus by the sixth post-operative day. Gastric suction and intravenous fluids were continued until the tenth day, when the bowel action returned. The drains were removed on the ninth day and the sutures on the eighteenth day, when the wound was soundly healed and the patient was eating normally.

He reported four weeks after discharge, and was symptom-free and on a full diet. A barium-meal examination on December 7 revealed a slight narrowing of the first part of the duodenum, probably as a result of the operation.

COMMENT

Closed traumatic retroperitoneal rupture of the duodenum is a rare injury. Johnson (1944) collected 52 cases from the literature between 1910 and 1943. The causative force may not necessarily be great, and the diagnosis of intestinal abdominal injury may therefore be delayed until signs of retroperitoneal sepsis or haemorrhage develop. When the parietal peritoneum of the abdomen is torn the signs of developing peritonitis may be the first indication of the diagnosis. In the case here reported the large retroperitoneal haematoma on the left side, associated with the free blood in the peritoneal cavity, no doubt explains the severe lower abdominal pain and tenderness in the left iliac fossa and probably accounted for so early a laparotomy.

The aetiology of retroperitoneal rupture of the duodenum is not clear. Cases of "burst injury" of the duodenum due to sudden compression of gastric contents with "blow out" of the duodenum have been described. This type of injury would be expected to cause a tear in the long axis of the gut. In the above case the tear was across the long axis and was most probably due to a sudden strain at the junction of the fixed and mobile parts of the first part of the duodenum associated with crushing against the vertebral column.

At operation, as pointed out by Simpson (1950), bile-staining of the retroperitoneal tissues should suggest a diagnosis and warrant inspection of this region. Simpson also recommends simple suture if possible, as was performed in this case.

Our thanks are due to Mr. G. H. Buckley for permission to publish this case.

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Reviews

A NAVAL OCCASION

Our National Ill Health Service: An Essay on the Preservation of Health. By Surgeon Vice-Admiral Sir Sheldon F. Dudley, K.C.B., F.R.S., Hon.LL.D.(Ed.), M.D., F.R.C.P., Hon.F.R.C.S.Ed., D.T.M., D.P.H. (Pp. 225. 15s.) London: Watts and Co. 1953.

Is this book meant to be taken seriously? One might regard it as a *jeu d'esprit* were it not that its distinguished author, who was Medical Director-General of the Royal Navy for the greater part of the war, is not the person to jest with sacred subjects. Its theme is that the N.H.S., which shows "appalling ineptitude after five years of brawling, obstruction and procrastination by all concerned," fails because it aims at cure rather than prevention; it should have been modelled on the medical services of the Forces, particularly the Royal Navy.

The thread of the argument, conspicuous enough in the first section, becomes less and less perceptible as the book proceeds until, before the middle is reached, it is irretrievably lost in a patchwork of bewildering variety and inconsequence—priority in medical discovery, anonymity in publication, unnecessary operations, the treatment of burns, the ethics of placebos and proprietary medicines, the inferior intelligence of Members of Parliament, and many other topics of lively interest but hardly to the point. For any evidence of consistent thought apposite to the subject one looks in vain. In the section on "The Preservation of Global Health," for instance, fulmination against the Civil Service and particularly the Treasury (whose staff should be trained not in the classics but in applied anthropology) leads straight to a discussion of world food production, the host-parasite relationship, and the damage done by the rabbit, moth, locust, rat, and prickly pear. Then follow field hygiene and its enforcement by health education and propaganda.

The author naturally gives great prominence to Lind, Blane, and Pringle, who, it will be generally admitted, from their Service experience taught civilian medicine the principles of prevention. But this happened in the eighteenth century. Sir Sheldon fails to mention that in both wars of the twentieth century the Royal Naval medical services had to be buttressed by the appointment of civilian consultants who were given the rank of admiral. He seems to forget, too, that naval personnel are highly selected for an age-period of maximum efficiency and discarded before degenerative and senile changes set in. Criticism of the Medical Man-Power Committee comes ill from a Service which might have been less wasteful of its own personnel.

The author admits the great advantage of naval discipline, but thinks its absence from civilian life can be remedied. The principles of health preservation are to be instilled into children at a tender age. He would like to see problem families put "into large establishments, under a firm but benevolent discipline such as that of the Services, whereby all sorts of bad or amoral, antisocial personalities become happy, self-respecting citizens." He admits, however, that this is impracticable until "fecklessness is made a punishable misdemeanour or certifiable as a dangerous form of mental deficiency." As if these remedies were not sufficiently draconian, a code of health morals would be laid down by a "panel of medical specialists assisted by experienced Law Lords." Among offenders would be those who sneeze in buses without covering their faces.

An epilogue deals with Utopias, uncongenial work, the harm which "meddlesome psychiatrists" might have done to Dr. Johnson, Charles Darwin, and Florence Nightingale, the use of leisure, and the obscure "as if" philosophy of Vaihinger. It ends with the strange belief that King Solomon was the most famous of all Freudians and that he was the author of *Ecclesiastes*.

Since this book was written the Government has appointed a commission to inquire into the medical services of the Forces. *Post hoc*, of course, but can anything be wrong?

FFRANGCON ROBERTS.

RESUSCITATION

Inhalation Therapy and Resuscitation. Meyer Saklad, M.D. American Lecture Series. (Pp. 338; 130 illustrations. £2 14s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1953.

Preventable anoxia as a direct cause of death is commoner than is generally believed. Not only in anaesthesia but in a wide range of diseases and circumstances this condition occurs, and its recognition, prevention, and treatment would undoubtedly save many lives every year. Dr. Saklad has cast his net wide to gather the material for his book. The physiology of respiration, the pathological effects of oxygen lack on every organ of the body, the treatment of a variety of conditions ranging from eclampsia to heat exhaustion and from intestinal distension to whooping-cough, the apparatus and technique of oxygen therapy, and the methods of artificial respiration and cardiac resuscitation—all these and many other topics too are to be found in some detail. The text does not make easy reading, for it is too often little more than a series of abstracts from the literature, but as a work of reference to the causes, results, and treatment of oxygen lack the book has no equivalent. It is well produced, the illustrations are clear and generally helpful, and an alphabetically arranged bibliography of some 402 papers and books is included.

This monograph is recommended to anaesthetists and others called upon to treat a patient suffering from oxygen lack. It is an invaluable book of reference to readers interested in the literature on anoxia.

W. W. MUSHIN.

SYNOVIAL FLUID

Synovial Fluid Changes in Joint Diseases. By Marian W. Ropes, M.D., and Walter Bauer, M.D. A Commonwealth Fund Book. (Pp 150. £1 5s.) Harvard: University Press. London: Geoffrey Cumberlege. 1953.

Over a period of more than twenty years Dr. Marian Ropes and Dr. Walter Bauer, with others of their colleagues at the Massachusetts General Hospital and the Harvard Medical School, have become well known for a number of outstanding contributions—both clinical and pathological—to our knowledge of joint disease. One aspect of their studies is summarized in this interesting book, which includes a large amount of hitherto unpublished material. Not only are their findings of great practical importance to those who are concerned with the diagnosis of joint diseases, but they are of interest in connexion with many problems of the physiology of synovial fluid formation.

Joint disease is usually marked by some degree of effusion, and ever since the introduction of chemical methods as aids to clinical investigation it has been hoped that analysis of aspirated fluid would provide information of help in diagnosis. Study of the present volume makes it clear that, although this has proved to some extent to be so, there are serious limits to the diagnostic possibilities of synovial fluid analysis. No individual chemical constituent of synovial fluid shows any change which is specifically diagnostic for a particular disease, although the pattern of change in a number of constituents broadly reflects the type and the extent of pathological change in the synovium of the involved joint. Even so, on the basis of their tabulated findings for 1,500 fluids, the authors suggest that the following determinations are sometimes clinically rewarding: viscosity; *p*H; cell count (total and differential); protein content; albumin:globulin ratio; sugar content; mucin content; and the type of mucin precipitate obtained on addition of acetic acid. Values for non-protein nitrogen, uric acid, and electrolytes—such as calcium, inorganic phosphate, and chloride—were not found to have any diagnostic significance.

The main purpose of the work is to show that joint diseases may be divided into two main groups on the basis

of synovial fluid findings. The first of these groups includes conditions such as traumatic effusions, osteoarthritis, osteochondritis, neuroarthropathy, and osteochondromatosis, where the joint fluid is clear and viscous, forms little or no clot, contains few cells—mostly lymphocytes, and mononuclears—has a relatively low protein content with a high albumin:globulin ratio, has a sugar content approximately the same as that of the blood, and gives a conspicuous mucin precipitate. Contrasting with these is the second main group consisting of all infectious arthritides and rheumatoid arthritis, where the fluids are turbid and less viscous, form large clots, contain many cells, most of which are polymorphs, have a high protein content with a low albumin:globulin ratio, show a sugar content lower than that of the blood, and give a poor mucin precipitate. It is suggested that the joint effusions in the first group have a common "traumatic" origin, and that effusions can thus be regarded as "traumatic" or "inflammatory." The main diagnostic value of chemical study is that it aids materially in distinguishing between these two large groups, although in a few conditions—notably rheumatic fever, pigmented villonodular synovitis, and gout—the fluid changes resemble each of the two groups in some respects.

H. A. SISSONS.

POLIOMYELITIS

Die Poliomyelitis. By Professor Stéphane Thieffry. (Pp. 328; 205 figures. 26.80 francs.) Bern and Stuttgart: Hans Huber. 1953.

This is a German edition of a French symposium published in 1950. It suffers from the unevenness of treatment characteristic of books formed from a collection of essays. The first essay, on epidemiology and immunology, has been brought up to date and is well documented in the text. It is as clear and balanced a short summary of the knowledge of to-day as I have yet read. After this the character of the book alters and the succeeding essays resemble more closely the chapters of a student's textbook and are devoid of references. The essays on the disturbances of respiration, muscle strength, and electrology are preceded by full discussion of the physiological basis of the respective subjects which at times is rather elementary. Their inclusion is useful for the student but swells the bulky volume unnecessarily. For example, the detailed description of the general chemical factors associated with muscular atrophy are not specific for poliomyelitis alone and could therefore have been compressed or omitted.

The book is illustrated by a series of line drawings which are most useful in the excellent section on testing muscle strength. Although the standard grading of muscle function is given, there are no comparative tables showing changes in muscle balance with convalescence. The orthopaedic section of the book is well illustrated and forms a sound résumé of the methods used with success. More important, it is dogmatic about what cannot be done with success.

While such a book, embracing as it does many specialties, cannot be expected to advance each one, it does give an overall picture of the disease and forms a sound student's manual. Many specialists would gain from it the advantage of a deeper insight into the problems of their co-workers on this distressing disease.

J. G. BONNIN.

EXAMINING THE PATIENT

Physical Examination of the Surgical Patient. By J. Englebert Dunphy, M.D., F.A.C.S., and Thomas W. Botsford, M.D., F.A.C.S. (Pp. 326; 188 figures. £1 17s. 6d.) Philadelphia and London: W. B. Saunders Company. 1953.

The tendency for the student to rely on laboratory tests and the *x*-ray examination in the diagnosis of surgical cases has often been deplored, but the only way to counteract it is to provide attractive books teaching him how to diagnose by his unaided senses. The authors quote Thayer: "Learn to see, hear, feel and smell and know that by practice alone can you become an expert," and in the preface they state that "this book is designed to focus attention on the methods and importance of eliciting physical signs in surgical conditions." They have undoubtedly succeeded in their aim, and we can cordially recommend the book to every surgical student.

The changing problems in diagnosis are indicated by the caution given that in infections of the hand "systemic signs may be completely abolished by vigorous antibiotic therapy although the local process may be progressing." The same warning is given in diagnosis of peritonitis: "The liberal use of the antibiotics greatly alters the signs of peritonitis. There may be very little abdominal tenderness, rigidity, or distension." This is a book to welcome and not to criticize, but we should like to see a fuller description of the signs of coxa vara, and Figures 57 and 38 are not in our opinion distinctive enough. English students need not worry about distinguishing the bite of the black widow spider in diagnosing acute abdominal conditions.

ZACHARY COPE.

MEDICINE AS A WHOLE

Modern Concepts in Medicine. By Julius Jensen, Ph.D. (in Medicine), University of Minnesota; M.R.C.S., L.R.C.P. (Pp. 636; illustrated. £4 6s.) London: Henry Kimpton. 1953.

Successful textbooks may come about for at least two reasons. A book may represent material which the author has practised and perfected through years of teaching students and appreciating their difficulties. Or it may represent a new and stimulating approach to a subject, as when Osler gathered together the clinical investigations and pathological observations of the nineteenth century into a single vividly written volume, or when McCallum wrote of pathology in all its manifestations as a process and not as something static. Jensen has tried to write this second type of book, but good intentions are not the same as achievement, and this must be frankly described as a disappointing book. Jensen's thesis is that medicine can be regarded as a consistent whole, in harmony with a general unitary conception of man's life and his destiny. The keys to this holist conception are to be found in Selye's work on stress, the theory of cybernetics, and the writings of philosophers such as Gerald Heard. So far so good, but when we get to the body of the book we find nothing new or fresh in this sense. The introduction is on cellular activity and principles of adaptation. The second part is entitled the "Essential Processes of Adaptation" and is on the various mechanisms of homoeostasis. Part III, "Structural Facilities in Support of Adaptive Processes," is internal medicine treated in the ordinary way. Part IV, "Cybernetics," deals with enzymes, vitamins, the endocrines, and the nervous system. The general impression is of material taken from standard textbooks of applied physiology and medicine which has been rearranged under new titles. The material is not illuminated with new ideas, and the book cannot be recommended for the ordinary medical reader.

L. J. WITTS.

PICTURES OF PARASITES

Synopsis of Medical Parasitology. By V. E. Brown, Ph.D. (Pp. 109; 103 figures. $3.50.) Wisconsin, U.S.A.: V. E. Brown. No date.

Although most of the drawings in this book are beautifully executed, it is regrettable to find that in many instances they are inaccurate in detail. To take but a single page (p. 102), we find that in the drawing of the microfilaria of *Loa loa* no cephalic space is shown, and that in the figure of a *Mansonella ozzardi* microfilaria nuclei are shown extending to the tip of the tail. In both cases these details of structure are taxonomically of great importance. These are not the only mistakes on the page. Little can be expected of a text that deals with trypanosomes in less than a thousand words, but the book is hardly intended to be more than a collection of drawings.

FERGUS J. O'ROURKE.

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TOXIC GOITRE

In October, 1863, Trousseau[1] was consulted by "a young married lady who habitually resides in Paris suffering from a subacute exophthalmic goitre." He was occupied with the idea that there would be some danger in giving iodine—and wrote iodine instead of digitalis on the prescription. When the patient returned in a fortnight her pulse rate had fallen from 150 to 90. Despite this fortunate accident Trousseau wrote in his subsequent comments that iodine generally does harm in Graves's disease. Not until 30 years ago did Plummer,[2] of the Mayo Clinic, reintroduce and popularize the use of iodine for hyperthyroidism, following it with thyroidectomy. Two other landmarks stand out in the treatment of thyrotoxicosis: the introduction of radioactive iodine, first recorded by Hertz,[3] and the discovery of the antithyroid drug thiouracil by Astwood,[4] also of Boston, in 1943. The clinician, who forty years ago had no effective therapy to offer in Graves's disease, is nowadays sometimes bewildered by finding that he has no fewer than three forms of treatment from which to choose. Like Bassanio in *The Merchant of Venice*, he is faced with a good deal of heart searching before he can decide in which of the three caskets he will find the right answer.

The cause of thyrotoxicosis remains unknown, though much evidence points to the anterior pituitary as the villain of the piece. Since this disease is subject to spontaneous remissions and occurs in widely varying degrees of severity, it may also present particular difficulties in diagnosis. For these reasons the introduction of techniques using radioactive iodine as a diagnostic tool is particularly valuable and is rightly emphasized in the Bradshaw Lecture delivered by Professor E. J. Wayne which we publish in the opening pages of the *Journal* this week. He reviews in comprehensive fashion the clinical manifestations of thyrotoxicosis and concludes that, while most of the classical signs and symptoms are a reliable guide to the disease in men, the diagnosis may be much more uncertain in women, especially at the menopause. Increased appetite, loss of weight, preference for cold weather, hot and sweating hands, persistent tachycardia especially during sleep, and hyperkinesis prove the most helpful diagnostic features. But there remains a group of patients in whom the diagnosis cannot be made with certainty, and then laboratory tests are necessary.

So many tests of thyroid function are available that it is clear that none is completely satisfactory. Estimation of the basal metabolic rate still remains the most useful test which is generally applicable, and when carried out with the careful technique described by Robertson[5] it is remarkably accurate. But the metabolic rate is raised in conditions other than thyrotoxicosis and may be difficult to determine accurately in the nervous woman; moreover, the test can be conducted satisfactorily only on the in-patient.

Serum protein-bound iodine estimations (P.B.I.) are exceedingly difficult to carry out and the technique is expensive and exasperating—except in the hands of such experts as Riggs.[6] The serum P.B.I. is a direct measure of the level of circulating hormone and therefore an excellent guide to hyperthyroidism; it is a pity that no simple method of determining it has been discovered. Cholesterol estimations[7] reflect indirectly the function of the thyroid gland and are of most value in assessing hypothyroid states.[8] Creatine and galactose tolerance tests vary too much in other pathological states to be of specific use in assessing hyperthyroidism.

Radio-iodine offers a unique way of measuring thyroid action, and it has deservedly become popular in clinics where many patients with thyroid disease are seen. It is idle to argue whether the B.M.R. or the radio-iodine uptake is a more accurate test of hyperthyroidism, since the two measure different functions of the gland. In fact all thyroid tests measure some aspect of thyroid metabolism, and a combination of them is more reliable than any single one. Radio-iodine has been used in many ways for measuring thyroid function. The rate of uptake in the gland can be obtained by placing a Geiger–Müller counter over the neck[9]; the amount excreted in the urine can be estimated from samples,[10] or the uptake in neck and blood stream can be compared. In addition radio-iodine offers an easy method of measuring the radioactive P.B.I. in the blood.[11]

[1] *Lectures on Clinical Medicine*, 1868, 1, 587. London: The New Sydenham Society.
[2] *J. Amer. med. Ass.*, 1923, 80, 1955.
[3] Ibid., 1946, 131, 81.
[4] Ibid., 1943, 122, 78.
[5] *Lancet*, 1952, 1, 511.
[6] *Pharmacol. Rev.*, 1952, 4, 284.
[7] Gainsborough, H., *Proc. roy. Soc. Med.*, 1935, 28, 989.
[8] Bartels, E. C., *J. clin. Endocr.*, 1950, 10, 1126.
[9] Pochin, E. E., *Lancet*, 1950, 2, 41 and 84.
[10] Fraser, R., *et al.*, *Quart. J. Med.*, 1953, 22, 99.
[11] Goodwin, J. F., *et al.*, ibid., 1951, 20, 353.
[12] *Med. J. Aust.*, 1950, 1, 139.
[13] *Lancet*, 1947, 1, 241.
[14] Moynihan Lecture, Royal College of Surgeons, 1954.
[15] Taylor, S., *Proc. roy. Soc. Med.*, 1953, 46, 242.
[16] Nickson, J. J., *J. clin. Endocr.*, 1948, 8, 1721.
[17] Cope, O., *New Engl. J. Med.*, 1952, 246, 368.
[18] *N.Y. St. J. Med.*, 1951, 51, 1633.
[19] Catz, B., and Starr, P., *J. clin. Endocr.*, 1952, 12, 228.
[20] *J. Hyg., Camb.*, 1927, 26, 1.
[21] *Medical Research Council Memorandum*, No. 18. H.M.S.O., London. 1948.

The treatment of thyrotoxicosis by long-term therapy with thiouracil compounds can now be fairly assessed after the first ten years of trial. If a patient is given thiouracil it is almost always possible to control the hyperthyroidism; later the disease can still be controlled with a much smaller dose. Poate[12] in Sydney and Himsworth[13] and others in this country have reported series of patients treated in this way. In this issue of the *Journal* Dr. J. F. Goodwin and his co-workers report at p. 422 the results obtained at Sheffield on 126 patients who were treated initially with thiouracil and a large number of whom have been maintained symptom-free for periods up to four and a half years. Their final conclusions are that about two out of every three patients will eventually relapse after withdrawal of treatment no matter how long that treatment is carried out. In view of this, such therapy can be recommended only for patients who live fairly close to a medical centre, since thiouracil may at any time cause agranulocytosis, and this will require treatment in a hospital if a fatal issue is to be avoided. The other disadvantages of long-term thiouracil therapy are that the thyroid gland enlarges, especially if the dose is not reduced early enough, drug rashes are fairly common, and unpleasant side-effects may be seen in individual patients.

The treatment of hyperthyroidism with radio-iodine is fairly new; the first patients were treated ten years ago, but they were few in number and a short-lived isotope, I^{130}, was usually given. To-day I^{131}, with a half-life of eight days, is in common usage, and many clinics have now been equipped to provide this kind of therapy. Speaking at the Royal College of Surgeons last month, Dr. George Crile, jun., of Cleveland,[14] stated that in his clinic hyperthyroidism, when not associated with a nodular gland, was now treated exclusively with radio-iodine. Over 1,000 patients have been so treated in the last five years, with a recurrence rate of about 1%. One disadvantage of this kind of therapy is that it is impossible to estimate the dose accurately, since this depends on the size of the gland. But the treatment has many advantages: the patient is spared an anaesthetic and operation and has only a short stay in hospital, and there is no risk of damage to the recurrent nerves or parathyroids. However, there remains the possibility that this therapy may lead to thyroid cancer. In the experimental animal there is quite good evidence that radio-iodine has a carcinogenic effect. Because of these findings many are unwilling to prescribe it for a patient under 40 years of age,[15] remembering that in the past the irradiation of skin led to malignant changes after a long latent period, often of the order of twenty years. At present the number of patients treated is too small and the time elapsed since treatment too short for a firm opinion to be given, but it appears unreasonable to give young patients this therapy.[16]

The surgical treatment of thyrotoxicosis has been greatly improved by preparing patients with the thiouracil drugs, so that now the mortality rate is negligible.[17] In addition the practice of removing at least seven-eighths of a toxic gland has reduced the recurrence rate of thyrotoxicosis to about 2%. There is no doubt that surgery offers the best form of treatment for toxic nodular goitre, for this is resistant to all kinds of medical therapy. If the patient with Graves's disease is prepared with methylthiouracil or neo-mercazole, and iodine is given in the immediate pre-operative period, the results of operation are good. In this week's *Journal* Dr. H.-J. B. Galbraith and his colleagues describe at page 420 the pre-operative use of iodothiouracil, which is a thiouracil compound containing iodine in its chemical structure. This drug has been in use for about five years now, and McClintock,[18] in Albany, and Catz and Starr,[19] in Los Angeles, have described large series of patients treated with it. The claim of the latter workers that this compound is more effective in hyperthyroidism than the administration of thiouracil and iodine separately has not been confirmed by other workers, and Doniach has shown histologically in the rat that iodothiouracil is less effective than either thiouracil or iodine alone. It seems, however, that if iodine and thiouracil are given concurrently or in combination, as described by Galbraith, excellent preparation is obtained for the surgeon.

The number of operations for hyperthyroidism fell precipitously with the introduction of the thiourea compounds, but it is now seen that they are climbing again as it becomes apparent that these anti-thyroid drugs when used for long-term therapy do not offer a very good chance of producing a remission. Radio-iodine is being used increasingly for this disease, but until another ten years has elapsed it is unlikely that many clinicians will be happy in using it extensively because of the risk of causing cancer.

The old observation, confirmed by Campbell[20] in 1927, that hyperthyroidism is commoner where there is endemic goitre seems to have been overlooked in Britain. There are many parts of this land where there is a relative iodine deficiency and simple goitre occurs, as shown by the Medical Research Council's report.[21] Despite the recommendation that salt should be iodized in this country, probably not more than 2% of salt consumed at present has this addition.

LUNG CANCER AND SMOKING

That there is a "strong presumption" of a causal relationship between smoking and cancer of the lung was conceded in Parliament by the Minister of Health[1] last week. The evidence on which this opinion is based came to a head with the publication in this *Journal* of the paper[2] by Doll and Bradford Hill in 1950, and was reinforced by their second paper[3] in 1952. The data have now been carefully assessed by a special panel under the chairmanship of the Government actuary (Sir George Maddex)[4] on behalf of the Standing Advisory Committee on Cancer and Radiotherapy, which in turn advised the Minister. As readers who followed the cautious and close-knit arguments of Doll and Bradford Hill might expect, these writers' conclusions from their own and others' researches[5] find ample confirmation in the statement that the Minister gave to Parliament. The evidence of some connexion between smoking and lung cancer may have received some additional support recently from the discovery by Wynder, Graham, and Croninger[6] that the experimental painting of mice with tobacco tar causes carcinoma of their skin. Moreover, some earlier experiments, also in the U.S.A., had shown that mice of a strain liable to develop lung cancer were more likely to develop it when exposed for a year to tobacco smoke than other mice of the same strain not so exposed.[7] The validity of these smoke experiments needs confirmation, and a series of somewhat similar experiments begun by the Medical Research Council 18 months ago will test the point. The strength of the evidence so far gathered together moved the tobacco manufacturers in the U.S.A. a month ago to set up a committee for research into lung cancer and smoking, and now British manufacturers have followed with the offer of a donation of £250,000 to the Medical Research Council, to be used at the Council's discretion.

Though so much evidence has been provided in Britain and the U.S.A. showing that some connexion exists between smoking and lung cancer, relatively much more is needed before a clear understanding of the connexion is obtained. No substance known to be carcinogenic to man, for instance, has yet been identified in tobacco, and this is one of the problems on which research is concentrated. The mouse carcinogen discovered by Wynder and his colleagues could prove to be misleading, a hazard to mice but not to men. Again, it is well known that some patients with lung cancer are non-smokers. Nor is tobacco smoke the only agent or condition associated with the causation of lung cancer, for Stocks[8] has shown that there is also a close association between urban residence and incidence of the disease. The possibility that townsmen smoke more than countrymen would seem to be insufficient to account for the disparity. On the other hand the principal and more positive facts known about lung cancer and smoking are broadly two: first, there is some kind of causal connexion; secondly, the risk increases with the amount smoked. In addition, cigarettes seem to carry a greater risk than pipes and cigars, and the risk attached to cigarettes may possibly be diminished by the use of filter tips or cigarette holders.

At a press conference held last week the Minister of Health wisely pointed out that it is not his duty or his Ministry's to speculate on the significance of the published reports, and he emphasized that research must be pursued with all vigour and speed. He considered the time had not yet come when the Ministry should issue public warnings against smoking, but, as his advisers pointed out, "It is desirable that young people should be warned of the risks apparently attendant on excessive smoking." The evidence perhaps allows medical men individually to go rather further than this and tell patients that there is probably an increased risk, to greater or less degree, associated with any amount of smoking, especially of cigarettes.

[1] See *Journal*, p. 465.
[2] *British Medical Journal*, 1950, **2**, 739.
[3] Ibid., 1952, **2**, 1271.
[4] The other members were Professor M. G. Kendall, Dr. W. P. D. Logan, and Dr. P. L. Mackinlay.
[5] Wynder, E. L., and Graham, E. A., *J. Amer. med. Ass.*, 1950, **143**, 329.
[6] *Cancer Res.*, 1953, **13**, 855. See *British Medical Journal*, December 19, 1953, p. 1362.
[7] Essenberg, J. M., *Science*, 1952, **116**, 561.
[8] *Brit. J. Cancer*, 1952, **6**, 99.

CHEMICALS IN FOOD

Agricultural chemicals used as insecticides, fungicides, and weed-killers have been in the medical news for the last few years. The dangers of some of these materials have been described, discussed, and, unfortunately, illustrated by cases of poisoning. In 1951 a working party under Professor S. Zuckerman reported[1] on the situation and made recommendations which have now been incorporated in legislation designed to reduce these hazards. No fatal or serious cases of poisoning were reported in this country during the past season. This satisfactory situation may be due not so much to the regulations as to the general alertness of the manufacturers and users, backed up by the watchfulness of the Government departments concerned.

Some of the chemicals used as pesticides may persist in crops and find their way in very small quantities into food. This possible danger is discussed in the second report[2] of the working party, which was reconstituted under the same chairman after finishing

its first task in 1951. It is not open to doubt that some of these chemicals are dangerous to those who use them. The doses received by men accidentally poisoned in this way are probably comparable in size to those causing signs of poisoning in experimental animals. The risks of consuming the very small quantities that could find their way into food are difficult, if not impossible, to measure. The dose likely to be taken in this way would probably be far below that capable of producing unequivocal changes in experimental animals.

Discussions on food are said to rank high on the list of subjects "having curious powers of robbing the speaker of his powers of logic,"[3] and members of the working party making this report have done well to retain their sense of proportion. The report gives an excellent survey of the situation as it exists to-day, and on the whole is reassuring. It contains an impressive list of materials that are used in pest control, including rodenticides. Incidentally, many will regret that the working party has not followed the lead of some other countries in condemning outright the use of bacterial cultures as rat poisons when there are other effective and safer rodenticides now freely available. In general the report states the facts or points out where ascertainable information is deficient and suggests how it may be amassed in the future. It wisely avoids adding more speculation to the question of possible health hazards arising from small quantities of chemicals in food, and begins by stating that no evidence has been presented "of any specific instances of illness which have resulted from eating such [treated] food. The position does not appear to have been established as one of immediate danger." Evidence and not mere opinion is needed before this assessment of the situation can be upset.

The working party then sought facts about the extent of the use of toxic chemicals in agriculture and the amounts that are actually present in food. These chemicals are not widely used in this country, but their use may become commoner as agricultural methods are modernized and efforts intensified. As to imported food, little information is available, and there is no control of the chemical treatment received during production, storage, and transit. Though some details might be obtained from analyses of food reaching this country, a much more satisfactory solution would be to organize some international exchange of information about the practices current in each food-producing country. The routine analysis of food is a widespread practice, but the search at present is mainly for the older and better-known poisons, such as lead and arsenic. The range of analytical control will have to be extended before we can obtain information about the quantities of the new chemicals in our food.

The working party recommends that a committee should be set up "to advise departments on problems relating to the risks to the consumer arising from the use of toxic substances in agricultural products and in the storage of food," and this recommendation has been accepted by the Government. If it fulfils the functions suggested for it, the advisory committee will gradually accumulate factual data on which future action may be based. When it has acquired some of these facts, it is to be hoped that it will be able to speak with authority on these new agricultural practices, so that a fully documented case can be made out for or against the use of any particular toxic material. Such authority is in fact badly needed in the whole field where chemicals are deliberately or accidentally added to food. Seevers,[4] for instance, has pointed to the impossibility of proving anything to be harmless and shown how scientific data have been distorted in attempts to make a case for or against the addition of this or that chemical to food. He writes:

> "It is almost axiomatic that areas of activity such as these in which *opinion* may substitute for lack of factual data may become the province of the crackpot, self-styled scientist, and the well-meaning but misinformed reformer, [who] may exert a powerful influence on the general public by posing as a champion of the individual safety and protector of the public welfare."

It is doubtful if the influence of any such reformer would ever equal or exceed that of a powerful commercial interest anxious to introduce a new material or technique into food production.

Several experts have suggested that decisions about the permissible chemical additions to food should be within the province of the medical profession, which, they think, is losing control of the situation. This presupposes that there are formulae that can be applied which will enable the doctor to decide whether or not a chemical will be harmful in given doses. But much still remains a matter of opinion. Mellanby[5] has suggested that some of the diseases of our modern civilization may be attributable to the effects of eating sophisticated food. Dodds,[3] taking an opposing stand, is apparently prepared to put his faith in animal tests to determine whether or

[1] *Toxic Chemicals in Agriculture*, 1951, H.M.S.O., London. Price 1s. 6d. net.
[2] *Toxic Chemicals in Agriculture—Residues in Food*, 1953, H.M.S.O., London.
[3] Dodds, E. C., *Lancet*, 1953, **1**, 1211.
[4] *J. Amer. med. Ass.*, 1954, **153**, 1329.
[5] Mellanby, E., *British Medical Journal*, 1951, **2**, 863.
[6] Meneely, G. R., *et al.*, *Ann. int. Med.*, 1953, **39**, 991.

not a substance is likely to be harmless. But it is difficult to interpret the findings of animal tests. Some would allow a large safety factor and expect a substance to be harmless to animals in doses exceeding by 10- or 100-fold those likely to be consumed by man. The results of some recent experiments in which sodium chloride was fed to rats[6] would lead, if such a formula was applied, to the condemnation of salt as a flavouring agent. In times of food shortage, rather than go hungry most people would cheerfully accept wheat contaminated with D.D.T. which had been added to prevent the depredation of insects. In other words, we must know the facts—be they political, economic, chemical, or biological—before we can assess what advantages will accrue from accepting an uncertain risk entailed by eating food containing foreign chemicals.

When an advisory committee such as that suggested by the working party has collected enough facts it may eventually frame a policy in which the use of chemicals in agriculture and food storage will come to represent a balance between productivity, cost, quality, keeping properties, nutritional value (for example, vitamin content) of the food and any possible risk of injury to health from chemicals persisting in the food. At least there is little question of the value of these chemicals in improving production and the quality of crops, whereas the benefits of some chemicals added to food during processing may be much more questionable.

BUCCAL CANCER

"Gentlemen," Sir Henry Butlin is supposed to have said to his students at St. Bartholomew's Hospital, "I shall not get cancer of the tongue. I neither smoke nor drink, my teeth have been removed, and I have never had syphilis." What is true for the aetiology of carcinoma of the tongue is also broadly true for the rest of the mouth. To these causes Butlin could have added leucoplakia, the importance of which as a precancerous lesion has long been recognized but the exact significance of which is still a matter for dispute. Two, at any rate, of these factors are less common now than they were at the beginning of the century, and it is therefore not so surprising that buccal cancer is one of the few types of malignant disease which appear to be on the wane. Certainly dental sepsis and patchy leucoplakia are found in the majority of patients with this disease, but it is equally true that it can occur in the cleanest of mouths. Squamous-celled carcinoma of the floor of the mouth is a rare condition (the term is made to include by some the inferior aspect of the tongue and by others the mucosal surface of the lower alveolus). Only 83 deaths were recorded from this cause in 1952 in England and Wales.[1] *The British Journal of Surgery* has now published the symposium on this subject read before the Association of Surgeons of Great Britain and Ireland in 1952 by Sir Stanford Cade,[2] Professor Brian Windeyer,[3] Mr. A. J. Gardham,[4] and Dr. J. L. Dobbie.[5] This valuable contribution puts on record the methods and results of treatment of a large number of patients from five of the hospitals which are justly renowned for their experience in the treatment of cancer. Cade reports on his patients at the Westminster and Mount Vernon Hospitals (97 patients in 25 years), Windeyer on the Middlesex Hospital group (131 patients in 20 years), Gardham on University College Hospital patients (72 patients in 27 years), and Dobbie on those from the Christie Hospital and Holt Radium Institute (427 patients in 12 years). If to these are added the figures published in 1950 by Ledlie and Harmer[6] on behalf of the Royal Cancer Hospital (190 patients in 10 years) an excellent survey of the subject may be obtained. But for the best interpretation of survival rates, as Miss Marion H. Russell discusses in an article at page 430 of the *Journal* this week, men and women should be considered separately, for women have higher survival rates than do men.

It is generally agreed that the early lesion is best treated by radiotherapy and the late primary lesion by surgical excision, particularly when the mandible is invaded by growth. Secondary nodes are dealt with on the same principles that govern their treatment when arising from primary growths in the tongue. Gardham calls attention to the fact, which is evident not only in the University College Hospital series but in the others as well, that the most diverse methods of treatment produce very much the same proportion of "cures." Thus, interstitial radium needling, double radium mould, and radium applicator-cum-teleradium all result in about 45% five-year survivals for the early cases with no nodes and 15% five-year survivals for the late cases with nodes. Some surgeons and radiotherapists are still willing and even anxious to argue the merits of their own particular choice of treatment. A more rewarding debate might decide which procedure gives the patient least tribulation. In any case the moral is clear: to get patients earlier and treat them effectively.

MILK AND MALARIA

Two years ago Maegraith and his colleagues[1] at the Liverpool School of Tropical Medicine were studying the metabolism of malaria pigment in rats kept on a special diet. Much to their annoyance they found that few of the malaria infections progressed normally: infections were either completely suppressed or of a low intensity, and this line of research had to be abandoned. These workers, however, quickly realized the peculiar significance of their results, and were able to demonstrate that a diet consisting of milk plus certain vitamins inhibited infections of *Plasmodium berghei* in rats. Not

[1] *Registrar-General's Statistical Review of England and Wales for* 1952, Tables, Part I, Medical. 1953.
[2] *Brit. J. Surg.*, 1953, **41**, 225.
[3] Ibid., 1953, **41**, 231.
[4] Ibid., 1953, **41**, 241.
[5] Ibid., 1953, **41**, 250.
[6] Ledlie, E. M., and Harmer, M. H., *Brit. J. Cancer*, 1950, **4**, 6.

long afterwards Dr. F. Hawking[2] attributed the phenomenon to deficiency of *p*-aminobenzoic acid in the diet. This substance (or some derivative) was found to be necessary for the growth of the parasite, and when it was added to the milk diet normal infections followed. Elsewhere in this issue Hawking has analysed the process in greater detail, and has shown that it is not quite so simple as he originally thought. The parasite is affected at the intracorpuscular stage when its nuclei are dividing—when it is metabolizing the haemoglobin. Rodhain[3] has found that piroplasms—which also live in red blood cells but do not require haemoglobin—are unaffected by deficiency of P.A.B. Likewise, Bray and Garnham[4] have shown that the pre-erythrocytic stage of mammalian plasmodia in the parenchyma cells of the liver is unaltered by a milk diet, possibly because the chemical processes accompanying nuclear multiplication at this stage do not involve haemoglobin. The malaria parasite is obviously very sensitive to slight changes in the constitution of haemoglobin: even minor alteration of the "sickling" type apparently inhibits growth of the parasite.[5] Incidentally, it is probable that a milk diet would fail to influence *P. elongatum* infections in birds because this malaria parasite lives principally in cells containing no haemoglobin: such an experiment might provide useful confirmation of the theory.

Hawking now points out that suppression of malaria by milk is a marginal phenomenon. Maegraith[6] had already reported that at certain seasons of the year the effect is not apparent, presumably because at these times the milk contains an extra amount of P.A.B. or derivative; and Hawking has found that the addition of P.A.B. to a nursing monkey's diet will permit the evolution of a normal infection of *P. cynomolgi* in the baby. On the other hand, he showed that the infection could be completely suppressed in a baby monkey whose mother was on a P.A.B.-deficient diet. The effect of a milk diet is discernible also in human malaria. The relative insusceptibility of African infants to this disease had been noticed for a long time, and Hackett[7] originally thought that it was due to possession by the child of an inherited immunity; but now a milk diet seems likely to be as important a factor. The effects in breast-fed infants are, however, inconstant and incomplete. Experiments in India[8] have recently shown that adults can be protected against *P. vivax* infections by living on milk alone.

The metabolic requirements of the malaria parasites are still so incompletely understood that the exact mechanism involved in this phenomenon remains unknown. Hawking points out that folic acid is as effective as P.A.B. in promoting the growth of *P. berghei*, and Fulton[9] has recently shown that cortisone also brings on a normal parasitaemia in rats on a milk diet. All those working on this subject have realized its importance to the chemotherapy of malaria, and Hawking reminds us of the way that drugs like sulphonamides or proguanil act in this disease by combining with or taking the place of the P.A.B. (or derivative) and thus depriving the parasite of an essential catalyst for its nuclear growth. This reaction can take place only when the parasite is in the blood; parasites living in liver cells are bathed in such a rich nutrient medium that such drugs cannot cope with the excess of catalyst and are therefore largely incapable of dealing with the tissue stages.

[1] *British Medical Journal*, 1952, **2**, 1389.
[2] Ibid., 1953, **1**, 1201.
[3] *Ann. Soc. Belge Méd. trop.*, 1953, **33**, 245.
[4] *British Medical Journal*, 1953, **1**, 1200.
[5] Allison, A. C., ibid., 1954, **1**, 290.
[6] Ibid., 1953, **2**, 1047.
[7] *Publ. Amer. Assoc. Adv. Sci.*, 1941, **15**, 148.
[8] Chaudhuri, R. N., and Chakravarty, N. K., *Bull. Calcutta School trop. Med.*, 1953, **1**, 8.
[9] *Lancet*, 1954, **1**, 162.

ASCITIC FLUID CIRCULATION

The peritoneal cavity normally contains only a few millilitres of free fluid, but in cases of hepatic cirrhosis or carcinomatosis peritonei the volume of peritoneal fluid often exceeds 5 and sometimes even 10 litres. This excessive accumulation is generally attributed to gross over-filtration of fluid in the splanchnic area. When in any given case the volume of the ascites remains stationary the reabsorptive mechanisms are keeping pace with production. It is only recently, however, that studies in both man and experimental animals have shown that ascitic fluid is far from being a stagnant pool, but, like so many other constituents of the body, is in a constant state of flux. The production of ascites in experimental animals by partial ligation of the inferior vena cava above the diaphragm has been closely studied by Whipple and his colleagues[1] with special reference to the protein constituents of ascitic fluid. Using plasma protein labelled by lysine containing C^{14}, they found that equilibrium between the ascitic fluid and the circulating blood was reached in one to two days in the case of albumin, and in something over two days in the case of globulin. Even more striking were the figures obtained by Prentice, Siri, and Joiner[2] for the turnover rate of the aqueous component of ascitic fluid. They gave intravenous or intraperitoneal injections of water labelled with tritium (radioactive hydrogen) to six patients with ascites, and recorded the passage of the radioactive water from the plasma to the peritoneal cavity and vice versa. Equilibrium was reached in about 10 hours, and from the slopes of the equilibration curves it was calculated that between 40 and 80% of the ascitic fluid present in any given case was exchanged every hour. Thus in a patient with 6 litres of ascitic fluid the daily turnover lies between 58 and 115 litres.

It has long been known that both fluid and particulate matter can be absorbed from the peritoneal cavity, but its capacity in this respect, demonstrated by the above experiments, is surprising. The results show that ascites can and does develop in the face of an absorptive mechanism capable of dealing with more than 100 litres a day. Figures for the turnover of peritoneal fluid in normal subjects are not at present available, but in view of those obtained by Prentice and his colleagues it is reasonable to attribute ascites to over-production rather than impaired removal of fluid. It is also apparent that only a slight displacement of the equilibrium can lead to rapid accumulation or equally rapid removal of the ascitic fluid.

[1] *J. exp. Med.*, 1950, **91**, 115. [2] *Amer. J. med.*, 1952, **13**, 668.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

THE CEREBROSPINAL FLUID IN DIAGNOSIS

BY

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The examination of the cerebrospinal fluid (C.S.F.) constitutes a very valuable method in the investigation of many diseases of the nervous system, and even in some general disorders. It often enables a firm diagnosis to be made, even while the patient is still at home, and this cannot but be of immense satisfaction to both practitioner and patient. The process of recovery in diseases hitherto fatal, but now yielding to treatment by antibiotics, can be followed with a fair degree of scientific accuracy by means of the examination of frequent samples of C.S.F.

The C.S.F. is nearly always obtained by lumbar puncture. It can also be collected from the lateral ventricles of the brain and from the cisterna magna, but these two sites should be punctured only when the patient is in hospital, where such facilities as an *x*-ray department and operating theatre are readily available. Discussion of such procedures has accordingly been omitted from this article.

The technique of lumbar puncture,* while relatively simple, does require practice and should be performed only after due consideration has been given to the benefits likely to accrue from this method of examination. Should the specimen be collected by the patient's own doctor it should be dispatched to the pathologist at once, as examination of the fluid should always be made without any undue delay. This is particularly important in a suspected case of meningitis, for both the cell count and the sugar content of the fluid will fall after a few hours. The C.S.F. pressure, the result of the Queckenstedt test, and the suspected clinical diagnosis should in such cases always accompany the specimen. This will help the pathologist to decide what examinations will yield the most satisfactory answers to the problem concerned.

Normal Cerebrospinal Fluid

It is necessary to know, first of all, exactly what constitutes a normal fluid. Table I shows the range of figures that can be regarded as normal for an adult. A few additional comments may be made. The cells are always lymphocytes in a fluid uncontaminated by blood, but if contamination has occurred one can assume that one polymorph may be present for every 500 red cells per c.mm.; never more than 4 and usually fewer than 4 cells per c.mm. are found. The level of the protein content—which is composed almost entirely of albumin and with only a trace of globulin—varies with age. A child should have 10 to 15 mg. of protein per 100 ml., while in an elderly adult a figure of 50–60 mg. per 100 ml. can still be regarded as normal. Similarly, prolonged immobility in bed will tend to raise the protein level. The chloride content may vary a little with the blood chloride, but the sugar level is fairly constant throughout the day, and it is not necessary therefore to collect the specimen while the patient is fasting.

TABLE I.—*Normal Cerebrospinal Fluid*

Pressure	125 mm. of water
Appearance	Clear and colourless
Cells	Up to 4 lymphocytes per c.mm.
Protein	Up to 30 mg. per 100 ml.
Globulin (e.g., Nonne–Apelt reaction)	Negative
Chlorides	700–760 mg. per 100 ml.
Sugar	50–70 mg. per 100 ml.
Lange test	No change
Wassermann reaction	Negative

The Lange colloidal gold test is empirical, and normally colour changes do not occur in any of the 10 tubes containing dilutions of C.S.F. Varying degrees of precipitation of the colloidal gold may occur, resulting in changes of colour, and these are recorded numerically from 1 to 5, the latter figure representing a complete loss of all colour in the supernatant fluid. There are two main types of abnormal curve: (1) the paretic, in which the maximum degree of colour change occurs in the first tubes—that is, in those of the strongest concentration of C.S.F.; and (2) the mid-zone or luetic curve, which shows a maximum change in the middle of the curve. Examples of each of these are described below. The C.S.F. pressure is normally about 125 mm. of water when the patient is in the recumbent position, and an increase takes place in cases of infection and when there is some space-occupying lesion inside the cranium. When the jugular veins are compressed in a healthy subject there is a rapid rise in C.S.F. pressure as recorded in the manometer, followed on release of the jugular pressure by a drop to the initial figure. This is known as the Queckenstedt phenomenon or test.

The clinical diagnosis and the results of the pathological examinations have always to be correlated, so that it would seem to be easiest to describe the results of the examinations under the headings of various disease processes.

Meningitis

There are three main types of meningitis—pyogenic, tuberculous, and virus. Table II shows the types of results that can be expected in each group. Naturally, the actual figures depend upon the stage of the disease reached when lumbar puncture is performed.

TABLE II.—*The C.S.F. in Meningitis*

	Pyogenic	Tuberculous	Virus
Pressure	Raised ++	Raised ++	Slight increase
Appearance	Turbid in varying degree	Clear or slightly opalescent	Usually clear
Cells	Hundreds or thousands	Tens or hundreds	4–200/c.mm.
Type of cell	Polymorphs	Usually more lymphocytes than polymorphs (2 or 3 to 1)	Lymphocytes
Protein	100+ mg./100 ml.	100+ mg./100 ml.	Up to 150 mg./100 ml.
Globulin	Positive	Positive	Positive
Chlorides	Decreased to about 650 mg./100 ml.	600 to 650 mg./100 ml.	Slight decrease—680 mg./100 ml.
Sugar	Absent	Decreased to 20 to 35 mg./100 ml.	Normal or only very slightly reduced
Direct smear	Causal organism	T.B. present	None
Culture	" "	" "	Sterile

In pyogenic infections, such as meningococcal or pneumococcal meningitis, the fluid which is turbid shows a considerable increase of cells, all of which are polymorphs. The chloride content is often reduced, although not to such a low level as in tuberculous meningitis, but this must not be regarded as a diagnostic feature. The reduction in the sugar content is of the utmost importance, and an accurate estima-

*See the article on this subject by Dr. William Gooddy earlier in this series (*British Medical Journal*, November 7, 1953, p. 1040).

tion should always be obtained. The fluid from cases of pyogenic meningitis shows a great reduction and often a complete absence of sugar. Effective treatment will always be reflected by a rise in sugar content, in fact this may precede the clinical improvement. The finding of the causal organism is vital, for it will indicate which antibiotic should be used. Prompt treatment is essential in all cases and is of special importance in pneumococcal meningitis.

The C.S.F. is less turbid in tuberculous meningitis than in the pyogenic group. There is an increase in cells, which are largely lymphocytes, although a small number of polymorphs are present in most cases. The chloride level is reduced in well-established cases, but may be almost normal in the early stages. The sugar content is early reduced, but this decrease never becomes a complete loss. Tubercle bacilli in the smears confirm the diagnosis. There is little doubt that they can be found in practically every case given enough care and time by the pathologist. Cultures or animal inoculation will confirm the smear findings after four or more weeks, but this delay is not permissible before initiating treatment. Again, a rise in the sugar level is the best guide to effective treatment, as intrathecal streptomycin will cause an increase in the cells and protein in the fluid, but does not affect the sugar level.

There are numerous viruses that are now known to affect the central nervous sysem, but all yield a somewhat similar C.S.F. picture. It is often difficult to distinguish between tuberculous meningitis, poliomyelitis, and lymphocytic meningitis in the early stages, but, by paying particular attention to the sugar and the results of the smear examinations, diagnosis should be possible. There are a few other conditions, such as sarcoidosis of the meninges and torulosis, both of which are very rare, that give rise to great difficulty in diagnosis.

Poliomyelitis

The C.S.F. varies with the stage of the disease, and in Table III are given the findings at the three most important stages. The noticeable feature in the pre-paralytic period is

TABLE III.—*The C.S.F. in Poliomyelitis*

	Before Paralysis	1st Week of Paralysis	Subsequent Weeks
Appearance	Clear and colourless	Clear and colourless	Clear and colourless, or with a coagulum
Cells ..	Can be up to 2,000/c.mm. (May be 25% polymorphs)	5–10 lymphocytes/c.mm.	Up to 4 per c.mm.
Protein ..	Normal or only slightly raised	Raised about 100 mg./100 ml.	Up to 300 mg./100 ml.
Globulin ..	Negative	Positive (+)	Positive (+)
Chlorides and sugar	Normal	Normal	Normal
Lange test ..	No change	0011210000	Normal or slightly mid-zone

the resemblance of the fluid, especially as regards the pleocytosis, to that found in tuberculous meningitis, except that the chlorides and sugar are normal. When paralysis occurs the cells decrease but the protein increases, and this increase may persist for some months. A fluid with a protein level of 150 mg. per 100 ml. or more may show a fibrin clot of the "spider web" type seen in tuberculous meningitis. Another point of importance is that, while polymorphs are commonly found in poliomyelitis, they are not seen in encephalitis.

Cerebral Abscess

The most characteristic features are to find a raised pressure, a pleocytosis of both lymphocytes and polymorphs, with normal sugar and perhaps normal or slightly reduced chloride levels, in a patient with infection of ear, frontal sinus, or lung. However, a deep-seated abscess may yield a C.S.F. similar to that found in a cerebral tumour in a similar site.

Encephalitis

The C.S.F. in the acute stage is under pressure, it is clear, and there is never a coagulum. A small lymphocytic pleocytosis with a slightly raised protein and a normal chloride content are found. The sugar level may be somewhat raised.

Syphilis

Primary.—A small proportion of patients with primary syphilis show a slight increase in the number of lymphocytes, together with a positive Wassermann reaction in the fluid before treatment. Few cases continue to give these findings after a normal course of treatment, but if these changes persist treatment should be continued, as in most instances the fluid will return to normal.

Secondary.—The C.S.F. shows an increase of cells up to about 50 per c.mm. composed almost entirely of lymphocytes, a slight increase in protein content, and a positive Wassermann reaction. The Lange test shows a mid-zone curve of the type 0012332100, but it is of no special significance. Rarely a spinal block caused by an inflammation of the meninges—an arachnoiditis—may be found, and give results similar to those seen in a spinal tumour, together with a pleocytosis and a positive Wassermann.

Tertiary.—There are three common types of disorder—namely, meningo-vascular syphilis, tabes, and general paralysis of the insane (G.P.I.). Table IV shows the results that

TABLE IV.—*The C.S.F. in Syphilis*

	Meningo-vascular	Tabes	G.P.I.
Pressure ..	Normal or slightly raised	Normal or slightly raised	Normal or slightly raised
Appearance	Clear and colourless	Clear and colourless	Clear and colourless
Cells	20–150/c.mm.	10–150/c.mm.	10–50 c.mm.
Type of cell	Mostly lymphocytes, few large mononuclears	Lymphocytes, a few large mononuclears	Usually lymphocytes and large mononuclears
Protein ..	Usually up to 100 mg./100 ml.	Usually up to 100 mg./100 ml.	50–150 mg./100 ml.
Globulin ..	Positive (+)	Positive (++)	Positive (++)
Lange test ..	Variable but usually mid-zone	Leutic, i.e., mid-zone (0012332100)	Paretic, i.e., 1st stage (5544322110)
Wassermann reaction:			
C.S.F. ..	+	++ (in 70%)	+++ (in 100%)
Blood ..	+++	+++ (in 65%)	+++

may be found in each of these conditions. It must be remembered that it is not always possible to place a patient in one of these categories with absolute accuracy following the first lumbar puncture, and it may be only after treatment or after a period of time that the correct diagnosis can be determined. The Lange test in particular does not always conform to pattern, and paretic curves such as 5544322110 may be found in meningo-vascular disease. Should, however, such a curve persist despite treatment a revision of the original diagnosis may be advisable. It is also noteworthy that a positive Lange curve of any pattern will change much more readily as a result of treatment in a patient with meningo-vascular syphilis than in either of the other two forms of this disease. The strength of the Wassermann reaction is indicated by the number of positive signs. Here again, treatment in meningo-vascular disease will reduce the strength of the Wassermann reaction faster in the C.S.F. than in the blood, and both will respond much more quickly in this type of disorder than in tabes or G.P.I. Fluids from these last two types of case may retain a positive Wassermann reaction in the blood or in blood and fluid, and an abnormal Lange test long after the patient improves clinically. The Wassermann reaction in the C.S.F. is positive in syphilitic conditions only, but a negative test does not exclude syphilis except for G.P.I. The other abnormal findings in the fluid in syphilis may be seen in some other conditions such as disseminated sclerosis, meningeal spread of a secondary carcinoma, sarcoidosis, and torulosis.

Congenital.—No alterations from the normal may be found in the fluid from some patients. Cases of clinical

tabes or G.P.I. will often show findings comparable to those found in acquired syphilis. Treatment only results in slow improvement in the pathological findings.

Disseminated Sclerosis

Characteristic changes may be found in this condition, one of which is a raised cell count of up to about 50 per c.mm. While lymphocytes largely predominate, a few fluids will also contain polymorphs in small numbers. The protein is rarely raised above 100 mg. per 100 ml., but the globulin test (Nonne–Apelt reaction) is almost always positive. The Lange test is abnormal in some 40–50% of cases and shows either a mid-zone or a paretic curve, the former occurring twice as often as the latter. The Wassermann reaction is always negative.

A paretic curve in the absence of a positive Wassermann reaction occurs only in disseminated sclerosis, inclusion-body encephalitis, and a few cases of encephalitis lethargica.

Cerebral Tumour

Lumbar puncture in cases of cerebral tumour is open to certain obvious dangers. Before removing C.S.F. it is essential to measure the fluid pressure, and to ensure by jugular compression, with a consequent rapid rise in pressure, that there is no herniation of the cerebellum into the foramen magnum. Great care must always be exercised in performing lumbar puncture in patients with a suspected cerebral tumour, and in general it is probably wiser to delay making this examination until the patient is in hospital, where operation can follow lumbar puncture should the need arise. Frequently the fluid pressure is raised, and any pressure above 200 mm. can be regarded as pathological. Examination of the fluid may show it to be quite normal. There is a raised cell count in some 5% of cases, which may be due to polymorphs as well as lymphocytes, and in a few cases even tumour cells may be found. The protein content is raised in some 75% of cases. On the whole the more innocent tumours tend to show a lower protein level, but there are exceptions to this rule. A glioma of the pons gives rise to a low protein, whereas a neurofibroma of the eighth cranial nerve is always associated with a raised protein content. Fluids from cases of tumours near the lateral ventricle have a higher protein content than do those associated with tumours above the tentorium and near the surface of the brain.

Spinal Tumour

The measurement of the C.S.F. pressure and the result of the Queckenstedt test are very important in this condition. There is no rise in pressure after jugular compression in a complete spinal block, while should the block be partial the rise will be slow, and the fall to the original level will also be slow. The initial pressure may, in fact, be low, figures of 40 mm. being not uncommon. The fluid, while it may be clear and colourless, is on some occasions straw-coloured and may clot spontaneously. Cells are not increased except in such conditions as meningeal sarcomatosis. The protein content is always raised in complete block, with figures even as high as 2,000 mg. per 100 ml. In partial block the protein content is raised, but rarely above 300–400 mg. per 100 ml. The Wassermann reaction is always negative, except in cases of syphilitic spinal arachnoiditis.

Other Conditions

There are numerous other disorders in which the examination of the C.S.F. may yield instructive results. For instance, in subarachnoid haemorrhage a fluid intimately mixed with blood will be obtained and, should the bleeding have occurred three days or more prior to lumbar puncture, the fluid after centrifugation will show a yellow coloration and a positive indirect van den Bergh reaction.

The examination of the C.S.F. for barbiturates in cases of poisoning by these drugs, and for urea and sugar in cases of coma from uraemia or diabetes, may also be mentioned as examples of some of the less common investigations that can be carried out.

The pathologist, provided he is aware of the possible clinical diagnosis, should be able, as a result of his examination of the C.S.F., to express a reasonably confident opinion on the nature of the disease process. There are, however, some neurological conditions which may still baffle both the practitioner and the pathologist, but these will probably be seen only at very infrequent intervals by any one practitioner.

Next article on Clinical Pathology.—"Simple Skin Pathology," by Dr. John O. Oliver.

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APPROVED NAMES

The General Medical Council has authorized the following "approved names" of drugs, selected by the British Pharmacopoeia Commission. The last supplementary list was published in the *Journal* of December 12, 1953 (p. 1321).

Approved Name	*Other Names*
Aminopterin sodium	Sodium 4-aminopteroylglutamate.
Bacitracin	An antibiotic produced by a strain of ***Bacillus subtilis.***
Benzathine penicillin	*NN'*-dibenzylethylenediamine di benzylpenicillin. "Dibencil," "Neolin," "Penidural," "Permapen."
Benzethonium chloride	Benzyldimethyl-*p*-(1:1:3:3-tetramethylbutyl)phenoxyethoxyethylammonium chloride. "Phemeride," "Phemerol chloride."
Dehydrocholic acid	3:7:12-Trioxocholanic acid. "Decholin," "Dehydrocholin."
Dichloroxylenol	2:4-Dichloro-3:5-xylenol.
Dihydrotachysterol	"A.T. 10."
Dyflos	Di*iso*propyl fluorophosphonate. "DFP."
Erythromycin	An antibiotic produced by a strain of *Streptomyces erythreus.* "Erythrocin," "Ilotycin."
Fumagillin	An antibiotic produced by certain strains of *Aspergillus fumigatus.*
Nicotinyl alcohol	3-Pyridylmethanol. "Ronicol" is the tartrate.
Pentolinium tartrate	Pentamethylene-1:5-bis-(1-methyl-pyrrolidinium tartrate). "Ansolysen."
Primaquine	8-(4-Amino-1-methylbutylamino)-6-methoxyquinoline.
Reserpine	An alkaloid obtained from *Rauwolfia serpentina* Benth. "Serpasil."
Sodium acetrizoate	Sodium 3-acetamido-2:4:6-triiodobenzoate. "Diaginol."
Tetracycline	4-Dimethylamino-1:4:4*a*:5:5*a*:6:11:12*a*-octahydro-3:6:10:12:12*a*-pentahydroxy-6-methyl-1:11-dioxonaphthacene-2-carboxyamide. "Achromycin."
Tretamine	2:4:6-Tri(ethyleneimino)-*s*-triazine. "Triethanomelamine," "Triethylene melamine," "TEM."

Reports of Societies

DENTAL ANAESTHETICS

At a meeting of the Section of Anaesthetics at the Royal Society of Medicine on February 5, with Professor R. R. Macintosh presiding, Dr. J. G. BOURNE challenged the present custom of regarding nitrous oxide as the mainstay of anaesthesia for out-patients. In his opinion the time had come for a fresh clinical assessment of this low-potency anaesthetic. He had therefore devised a method by which the reactions of patients could be observed after nitrous oxide had developed its maximum effect (after 10 or more minutes). Only 1 in 4 out of 60 unselected adult patients investigated in this way reached surgical anaesthesia. In a further 1 in 4 patients Dr. Bourne was not even convinced that unconsciousness was present, though these patients remembered nothing. More than half the patients retained reflexes that were too brisk to allow even minor operations.

Saturation of the brain with nitrous oxide took time (periods varying from 7 to 15 minutes had been suggested). But the majority of out-patient dental operations, including induction of anaesthesia with nitrous oxide, were completed within two minutes. Armstrong, in his book on aviation medicine, had given the explanation why this method worked. He had written: "A man at rest can hold his breath for 1 to 1¼ minutes. But if the oxygen in the lungs and blood is washed out by breathing any inert gas such as nitrogen, sudden and complete loss of consciousness will occur in about 50 seconds." Armstrong had recorded the times taken for pilots to lose consciousness when cut off from their oxygen supply at high altitudes and left breathing air, and his figures had led Dr. Bourne to the conclusion that "the expert with nitrous oxide, knowing the trick, induces 'anaesthesia' rapidly by taking his patients straight to 30,000 or 40,000 ft.* From there he allows them to descend only so long as they behave themselves and then only at a rate that is compensated by the accumulation in the central nervous system of increasing quantities of nitrous oxide."

Anoxia Plus Nitrous Oxide

In some patients not resistant to nitrous oxide a light plane of anaesthesia could be reached by the summation of two effects—anoxia plus nitrous oxide. As nitrous oxide accumulated in the brain more and more oxygen could be added and anoxia was gradually relieved. But with the large group of patients who were semi-resistant the position was not so happy. As several authorities had noted, anaesthesia demanded a restriction of oxygen supply (according to Kaye a "gross" restriction). Clement had written: "Control of anaesthesia is synonymous with control of the oxygen."

True resistance was seen in patients who were barely unconscious even when saturated with 80% or 90% nitrous oxide. It seemed to come from habituation to narcotic drugs, and was commonest in middle-aged and elderly patients—those in whom deprivation of oxygen would seem most unwise. Anoxia of the severity required to produce unconsciousness in these patients did not leave much room for bungling. Courville had shown that the anoxic decerebration of nitrous oxide anaesthesia could be irreversible. Some degree of damage to the brain might pass unnoticed in many cases. Though anoxia was recognized as harmful and was avoided in in-patient anaesthesia, in out-patient practice it was still employed by all and sundry as a supplementary, or perhaps even a main, agent of anaesthesia.

After asking whether nitrous oxide, as commonly used in out-patients, was a suitable introduction to anaesthesia for undergraduate medical and dental students, Dr. Bourne then described (with the help of an admirable film) the advantages of a method of out-patient anaesthesia with cyclopropane. Using a large reservoir bag (1.3 gallons—4.6 litres), with 50% cyclopropane in oxygen, he had anaesthetized 1,918 patients of all ages without mishap. Induction was very quick: all patients lost consciousness in 3 to 6 breaths, and after a few more breaths were ready for operation. By this means a maximum effect was produced with a minimum amount of drug.

The possible disadvantages of cyclopropane as an out-patient anaesthetic were threefold: first, salivation might occur, but was easily prevented by giving 1/75 gr. (0.86 mg.) of hyoscine hydrobromide, or half that dose to children, 40 minutes before operation; secondly, recovery might be delayed; and, thirdly, post-anaesthetic nausea and vomiting might occur.

Nausea and vomiting delayed recovery, but they could largely be avoided if the mixture of cyclopropane was breathed for only one minute. This gave satisfactory operating conditions for about 2½ minutes; if necessary the period of anaesthesia could in most cases be extended by administering nitrous oxide (80%) and oxygen after induction with cyclopropane. In Dr. Bourne's series of patients recovery was rapid, and 4 out of 5 of those who had previously had "gas" expressed a decided preference for cyclopropane. He claimed that, provided the duration of cyclopropane inhalation and its concentration were controlled as he had indicated, this technique might be safer in the hands of a novice than nitrous oxide. Nevertheless, nitrous oxide anaesthesia carried a very low mortality, and any method recommended as an alternative must be given a thorough clinical trial and no danger overlooked. The time had now come when the whole subject of anaesthesia for the out-patient should be reviewed.

Discussion

In the discussion that followed Mr. ROBSON said that from a dental surgeon's viewpoint the cyclopropane mixture was far preferable to the usual dental "gas." Bleeding was less and, most important of all, the patient was motionless. In short, the dentist received ideal conditions, and it was to be hoped that the day would come when nitrous oxide would be discontinued—the sooner the better.

Dr. VICTOR GOLDMAN pointed out the danger of attaching too much importance to the weak anaesthetic properties of nitrous oxide if the patient had previously been breathing a high percentage of oxygen. The nitrous oxide–oxygen mixture must be defended. He recalled that Clement claimed that the majority of "gases" were ruined by giving too much oxygen at the start, and yet even more were spoiled by not giving enough oxygen once the patient had lost consciousness.

Dr. G. S. W. ORGANE stressed the importance of the danger of an explosion with cyclopropane. He thought it might be possible for a spark between the dental forceps and a filling in the patient's mouth to ignite the anaesthetic mixture.

Dr. J. D. LAYCOCK felt that more thought should be given to the use of trichlorethylene in out-patient anaesthesia. In his experience trichlorethylene was capable of producing suitable anaesthesia even when used with "a rag and bottle."

Dr. R. BLAIR GOULD claimed that the dangers of nitrous oxide as a dental anaesthetic were exaggerated. Very few people could not be given nitrous oxide and still be kept "pink" during the two or three minutes of a dental operation. Resistant patients should be given a little premedication.

In a brief reply Dr. BOURNE countered any criticism of cyclopropane as an out-patient anaesthetic by saying, "The patients prefer it, the surgeons prefer it—so why use anything else?"

*9,000 or 12,000 metres.

Correspondence

Early Treatment of Cleft-lip and Cleft-palate

SIR,—I do not agree with Mr. W. G. Holdsworth (*Journal*, February 6, p. 304) that in double clefts of the lip there is usually "a serious deficiency of tissue." I know this belief is widely held, and it has led to some surgeons advocating what is to me the horrifying procedure of a "primary Abbé" operation—that is to say, transplanting a part of the normal lower lip into the alleged deficiency of the upper.

In my opinion the meagre, tight, and immobile upper lips which result from the classical operations are due to fundamental faults of principle and technique. These are: (1) Not correcting the displacement of the premaxilla, if this is present. To do this it is necessary to understand what pushes it forward—the prevomerine bone—and to remove this alone. (2) Not getting junction of the premaxilla with the rest of the alveolar ridge. If this is not done it will atrophy. (3) Not forming the labio-gingival sulcus at the start. If this is not done the lip is tethered down and immobile, and the muscles cannot develop. (4) Not obeying the primary orthopaedic principle of joining the actual ends of divided muscle. All classical procedures join one end of the orbicularis oris to one side of an inert central piece of tissue, and the other end to the other side. Imagine what would happen were a ruptured quadriceps to be treated in the same way. (5) Not understanding the embryology of the lip. Embryologists have not noticed that there is an interesting minor problem to be solved in how the mouldings of the normal lip are produced by the fusion of its various primary parts. I think it is possible to work this embryology out, to translate the process into a geometrical formula, and finally to interpret this in a surgical proceeding.

I have published large-size unretouched photographs, without lipstick and without smiles, showing the results of treating double hare-lip with displaced premaxilla in two operations.[1] If those who use other methods would do the same we would be able to judge how we stand.—I am, etc.,

London, W.1. DENIS BROWNE.

REFERENCE

[1] *Ann. roy. Coll. Surg. Engl.*, 1949, 5, 169.

SIR,—Mr. W. G. Holdsworth, in his article on the "Early Treatment of Cleft-lip and Cleft-palate" (*Journal*, February 6, p. 304), states: "Little is known of the effects of operation on the development of the facial skeleton, and these may be serious enough to prohibit procedures otherwise commendable." The essential problem which requires solution is whether the deviation from the normal growth pattern seen in the adult patient who has undergone surgical closure of a cleft lip and/or palate in infancy represents the mature development of an intrauterine defect, or the end result, which in some cases almost amounts to a mutilation, of surgical interference with growth centres, either directly from the operative procedures, or indirectly from restriction of the normal downward, forward, and lateral projection of the middle third of the facial skeleton by its enclosure in a vice of scar tissue.

Contrary to Mr. Holdsworth's statement, the whole question of the effects of operation for closure of cleft lip and/or palate defects on the development of the facial skeleton has been carefully and comprehensively studied since 1931 in the United States. The investigations carried out have not been confined merely to the dental arches, but have embraced the entire facial skeleton. The technique utilized was that of cephalometric roentgenology by means of the Broadbent-Bolton cephalometer, a method which employs a series of antero-posterior and lateral radiographs of the skull exposed and positioned under standardized conditions so that accurate determinations of the growth pattern may be carried out by anthropometric and cephalometric measurements.

Foremost among the conclusions derived from these investigations is the fact that five-sixths of the total palatal breadth have been accomplished by the end of the fourth year in normal individuals, with total width increments by the end of the tenth year. The other major points of interest can best be summarized by reference to the observations of Slaughter and Brodie,[1] whose deductions are based upon a study of 1,349 cases. They state: "The evidence is already at hand that surgery can and does inhibit normal growth. This interference is directly proportional to the amount of injury to growth centres and to diminution of blood supply to the parts concerned. Other evidence is available to show that congenitally deformed parts, unless permanently damaged, grow at normal rates. These two findings alone should cause us to examine our concepts and procedures very carefully. Together they indicate that surgery, poorly executed or poorly timed, can do more damage than good in the long run."

The only advantage claimed for operation on the palate before the age of 9 months is that the child will ultimately have a much better chance of achieving normal speech later. Mr. Holdsworth refers to "the inadequacy of any classification based upon personal appraisal of cases," and this sense of inadequacy would appear to be particularly pronounced when it comes to the assessment of what constitutes apparently faultless speech. The evidence that better speech results from closure of the palatal defect before the age of 5 is largely based upon the auditory impressions of the operators themselves rather than upon impersonal scientific facts, which latter observations have at least established beyond reasonable doubt the price which must be paid when the debt of early operation is redeemed in adult life. A rough translation of the words of Veau and Borel quoted by Mr. Holdsworth would be: "The minor details of the lip which often attract all our attention, have not the same importance as the general appearance of the face which occupies us less." To which I would like to add the suggestion that the minor details of the differences in clarity of enunciation between cleft-palate patients operated upon at different ages have not the same importance as the major differences in the ultimate appearance of the face and jaws which ensue from surgical interference during the period of maximum growth of the maxillae—that is to say, the first four years of life.

The results which may be anticipated from the careful and meticulous technique employed by Mr. Holdsworth may ultimately be very much better than those hitherto performed by less delicate operators, but any attempt to advance the age of operation upon a cleft-palate must be deplored by those who have studied or carried out careful investigations into the ultimate sequelae of such a procedure.—I am, etc.,

Basingstoke. N. L. ROWE.

REFERENCE

[1] *Angle Orthodont.*, 1949, 19, 223.

A Cosmetic Amputation

SIR,—It was a pleasure to see the letter of my friend and former teacher, Hamilton Bailey, on this subject (*Journal*, January 30, p. 275). From my experience I can support what he said. He taught me this amputation over 20 years ago, and since then I have practised it. It has always been pleasing to see these patients afterwards—they have had good functional and cosmetic results. Amputations where the head of the metacarpal has not been removed have always seemed to me unsightly, and for several patients I have re-operated to remove the "odd" prominence.—I am, etc.,

London, W.1. HAROLD DODD.

Mucocele of the Appendix

SIR,—Mr. J. H. Johnston's article (*Journal*, January 16, p. 135) stimulates me to report a case of mucocele of the appendix with pseudomyxoma peritonei.

The patient was a para one, aged 30, whose only complaint was of a mucous vaginal discharge which appeared to be due to an excessive cervical secretion. The uterus was in fixed retroversion and there was a small cyst of the left ovary. Further questioning revealed some discomfort recently in the lower abdomen and back a few days before her periods. A diagnosis of pelvic endometriosis with a chocolate cyst of the ovary was made, and the discharge considered to be due to pelvic congestion.

At laparotomy about 10 oz. (284 ml.) of "mucin" was found lying free in the peritoneal cavity. The uterus was bound down in retroversion by extensive pelvic endometriosis, and there was a small chocolate cyst of the left ovary. The right ovary appeared normal. The appendix was grossly thickened throughout its length, and surrounded by myxomatous tissue which appeared to be coming from a perforation in the appendix which was neither constricted nor kinked, and I removed it with a small cuff of caecum. The ovarian cyst was enucleated, and the uterus anteverted by means of a Gilliam suspension.

I am grateful to Dr. Whitelaw for the following histological report. "Ovarian tissue shows a follicular cyst filled with blood clot. Section of appendix is cyst-like in character with diameter of lumen 1.0 cm. In the specimen there is no occluding stricture. The wall is composed of a lining of high mucus-secreting columnar cells. There are no remains of cysts, and lumen is filled with mucin material with a few scattered cells. The submucosa is narrowed, fibrous, and has a few scattered lymphoid follicles. The muscular coat is of considerable thickness (1.7 mm.) and in two places is ruptured or deficient, and the mucous contents pour through and infiltrate the peritoneal coat. The cells associated with the 'mucin' are plasma cells and round cells and a few foreign body giant cells. There are no cells of epithelial origin in this over-spill."

The patient had an uneventful convalescence, and subsequent questioning failed to elicit any history that could have been construed as appendicitis. The muscle hypertrophy and the perforation would conform with Wilson's theory of appendiceal diverticula,[1] which in the absence of a constriction must represent the continuous efforts of the appendix to expel its unusually profuse and viscous secretions.

I have called this case a pseudomyxoma peritonei, but if we accept Woodruff and Macdonald's classification of benign and malignant mucocele[2] this is really only a *pseudo* pseudomyxoma peritonei. We are so little conversant with the real mechanism of this condition that I do not agree with Mr. Johnston's suggestion of post-operative radiotherapy for these cases, particularly if the patient happens to be a young woman, unless the pseudomyxoma is seen to recur. Pseudomyxoma due to cystadenoma of the ovary requires separate consideration, which space does not permit.

I saw this patient recently, four months after the operation. There is no evidence of recurrence. She is now free of all discomfort at her period times, but her mucous vaginal discharge persists, and I shall now try a small "office procedure" which includes the use of a silver-nitrate stick.—I am, etc.,

EDWARD COPE.

Birmingham, 18.

REFERENCES

[1] *Brit. J. Surg.*, 1950, **38**, 65.
[2] *Surg. Gynec. Obstet.*, 1940, **71**, 750.

Immunization Against Tetanus

SIR,—I was interested to read in your leading article entitled "Combined Prophylactics" (*Journal*, December 12, 1953, p. 1313) a suggestion that active immunization against tetanus should be offered to schoolchildren. It is not generally realized that all Service recruits receive on enlistment full active immunization with three doses of tetanus toxoid. The Services laboratories consider that this confers a safe level of immunity for about four years, when a further boosting dose is necessary. After completing their National Service a high percentage of young men who meet with accidents will already have a reasonable level of immunity. Before giving an injured man anti-tetanus serum I think it is always worth while to ask about previous Service inoculations. No Serviceman will have missed having his doses of tetanus toxoid unless he has deliberately "refused" them, and this fact he will certainly remember. Within ten years of active immunization one boosting dose of tetanus toxoid should then be adequate. I have recently encountered several examples when Servicemen in uniform were given "3,000 A.T.S." by casualty officers.—I am, etc.,

G. M. BAILEY.

Sonning-on-Thames.

Ulcerative Colitis

SIR,—Just a few lines in reply to Dr. Norman P. Henderson (*Journal*, January 30, p. 277). All my patients were examined by the sigmoidoscope and opaque enema before operation, but I thought these elementary precautions so obvious as not to require mention. The conditions which may be mistaken for true ulcerative colitis and to which Dr. Henderson rightly draws attention were, therefore, as far as possible excluded.

I was flabbergasted to read that Dr. Henderson regards ileostomy as only a preliminary to colectomy. I have seen some of the results of the latter operation, not that I was ever guilty of recommending it myself, but a good many years ago it was rather a favourite procedure of the late Sir Arbuthnot Lane, who regarded the colon as a sort of cesspool and the *fons et origo* of a mythical condition "auto-intoxication"—then almost as popular a diagnosis as "allergy," "endocrine-imbalance" (odious term), or "disk lesion" is now. (Odd, by the way, how every generation of our profession has its favourite diagnoses. Looking back over the past 60 years I can recall many such, each of which has had its little day and ceased to be, and if I might venture to give the young doctors of to-day a piece of fatherly advice I would say: Beware of the fashionable diagnosis.) Well, I often saw the end results of Lane's activities, and, apart from any question of immediate operative mortality, they were sometimes, in the idiom of to-day, "pretty grim." Dr. Henderson had best be careful, therefore, lest the last state of his patients be worse than the first, even if he does prevent an occasional one from developing cancer later on.—I am, etc.,

ROBERT HUTCHISON.

Streatley, Berks.

Fatal Bronchial Asthma

SIR,—The most important fact brought out again by Drs. C. K. Robertson and K. Sinclair (*Journal*, January 23, p. 187) is the necropsy finding of bronchi blocked by mucous plugs in all cases. The practical conclusion from this is that the mucus must be removed by treatment. The effect of a trypsin aerosol as reported in two American papers quoted by your annotator (p. 203)[1 2] scarcely justifies his optimism. One of the authors has not treated asthmatics, and the other stresses that the treatment was ineffective in chronic asthma. Neither has made any attempt to assess objectively the effect of trypsin on expectoration.

Nor do I agree with Mr. A. M. Zamora (*Journal*, February 6, p. 333) that treatment should be suction through the bronchoscope. This rather drastic method might give partial relief for a short time, but not all bronchi, and particularly not the smaller ones, are cleared by it. Moreover, the treatment cannot be repeated every few days. The aim of treatment for patients who continue to produce large amounts of sticky mucus must be to liquefy the mucus. This can be done efficiently by iodine, given either in the form of Lugol's iodine, as Drs. Robertson and Sinclair suggest, or as potassium iodide 15 gr. (1 g.) three times a day or more. Iodine sensitivity is infrequent in asthmatics and can be overcome by drastic reduction of dosage. Myxoedema[3] is rare and can be countered by thyroxine. Treatment with iodine is indeed so efficient that neither Pines[4] nor I[5] have had to resort to bronchoscopy in any case of asthma.—I am, etc.,

H. HERXHEIMER.

London, W.C.1.

REFERENCES

[1] Limber, C. R., *et al.* (1952). *J. Amer. med. Ass.*, **149**, 816.
[2] Unger, L., and Unger, A. H. (1953). Ibid., **152**, 1109.
[3] Morgans, M. E., and Trotter, W. R. (1953). *Lancet*, **2**, 1335.
[4] *J. Amer. med. Ass.*, 1950, **142**, 537.
[5] *Management of Bronchial Asthma*, 1952. Butterworth, London.

Chronic Bronchitis

SIR,—I read Mr. John Fry's article on chronic bronchitis (*Journal*, January 23, p. 190) with great interest. That the death rate in Great Britain should be so much higher than any other country certainly suggests that the subject requires further investigation.

It seems possible that the distribution of the disease and the morphology of the bacteria and/or virus involved might prove a useful angle of approach to the problem. In America (New England) the incidence of chronic bronchitis is higher in rural districts than industrial areas, and in England, if we exclude pneumoconiosis, we may find that rural districts have a high incidence, and I think this has been established in the Thames Valley. Is there a factor in the environment of bacteria and/or virus which increases their virulence? How is it that scarlet fever is commoner in late summer and autumn, that measles is prevalent in the winter and spring, that influenza has periodic pandemic waves, and that smallpox apparently spreads sometimes by convection? What is the factor that determines a harmless saprophyte such as *B. coli* becoming a virulent germ?

Modern entomological books provide distribution maps of insects, and, although their pabulum may be widespread, the insects are found in more or less restricted areas. May not the flora of the bronchial tree be also restricted by certain unknown laws? Some years ago it was found in a large town that cases of rheumatism in children were largely restricted to the areas around the submerged rivers of the city. No doubt immunity and heredity play their part in resistance to infection, but is there not a case for the factors that increase the virulence of the germs?—I am, etc.,

Tarrington. H. G. LANGDALE-SMITH.

The Normal Blood Count

SIR,—In his excellent article under the heading "Clinical Pathology in General Practice" (*Journal*, February 6, p. 326) Dr. George Discombe states that the mean corpuscular haemoglobin concentration is obtained by dividing the haemoglobin concentration in grammes per litre by the packed cell volume. I suggest that this should be calculated by dividing the haemoglobin concentration in grammes per 100 ml. by the packed cell volume and multiplying by 100.—I am, etc.,

Haywards Heath. R. W. P. JOHNSON.

SIR,—Dr. George Discombe's article on "The Normal Blood Count" (*Journal*, February 6, p. 326) was helpful and stimulating. He rightly emphasizes the value of inspection of the stained film in the study of red cell abnormalities, and he says that the film shoud be "so thin that the cells are separate." This does not go far enough, for it does not exclude parts of the film which are too thin, notably the very last part spread. Here the cells are separate, but they are mechanically distorted and so flattened that the normal central pallor is not seen.

Red cells should be studied in parts of the film which are a little thicker than the thickness of a red cell. In such a place a few of the cells in a field will be slightly overlapped by other cells, but most will be uncovered. Such parts of a film are excellent for studying the morphology of both red and white cells (but are not suitable for white cell differential counts).—I am, etc.,

London, W.2. R. R. WILSON.

Controlled Hypothermia

SIR,—We were relieved to see from his comments on the letter from Drs. J. W. Dundee and T. Cecil Gray (*Journal*, January 30, p. 272) that the writer of the annotation on "Chlorpromazine for Hypothermia" (*Journal*, January 9, p. 89) realized his error in assuming that we believed the drug to be a ganglion-blocking agent. It is clear, however, from his further remarks on regulation of body temperature and the autonomic system that we differ in our conceptions of what structures constitute this system. While it is quite true that from a strictly anatomical point of view the autonomic nervous system is simply an efferent outflow with two groups of peripheral pathways, sympathetic and parasympathetic, it has not seemed unreasonable to us to take a broader view of it. Physiologically it may be regarded as the system which effects those adjustments necessary to maintain constant the internal *milieu* in the face of a changing external environment.

Holding this view, we feel that it is quite logical to include in our conception of the autonomic system these centres in the hypothalamus and elsewhere which co-ordinate and integrate the functions of this system. Ample evidence exists that heat-regulating centres are present in the hypothalamus.[1] It is here as well as on other centres that we have supposed chlorpromazine to act, and in using the term autonomic block we intended to refer as much to this action of the drug as to its adrenolytic effect.—We are, etc.,

P. R MESHAM.
W. E. B. SCOTT.

Liverpool, 7.

REFERENCE

1 Ranson, S. W. (1940). *Res. Publ. Ass. nerv. ment. Dis.*, **20**, 342.

Sterilization of Ampoules

SIR,—It is inevitable that words of wisdom must fall on stony ground, for Dr. G. C. Steel (*Journal*, February 6, p. 335), alas, has missed the point, not only of correspondence which litters the literature, but also of the inferences to be drawn from Professor L. P. Garrod's excellent letter (*Journal*, December 5, 1953, p. 1269).

As the subject of "sterilizing ampoules" is fast becoming tedious, may I just ask Dr. Steel at least to examine his opened ampoules, preferably before intrathecal injection? Even if he does not believe that bacterial contamination of an intact ampoule can occur, the fragments of unsterile glass occasionally reposing in the bottom of his unsterile opened ampoule will doubtless be an object lesson to him.—I am, etc.,

Edgware. D. RECKLESS.

Sedimentation Rate in Active Tuberculosis

SIR,—In his article on "The Laboratory Diagnosis of Pulmonary Tuberculosis" (*Journal*, January 30, p. 267) Dr. J. W. Clegg includes the sentence: "The sedimentation rate is always raised in active tuberculosis and falls as healing takes place." The article is one of a series giving excellent advice or instruction, and maintains the high standard which has been set. Consequently many who have read it will be likely to place great reliance on the statements made, and there is a danger that it will be assumed that the absence of a raised sedimentation rate excludes a diagnosis of activity of a tuberculous lesion. While it is true that the sedimentation rate is *usually* raised in active tuberculosis, active disease can exist in its absence. In 287 cases of active pulmonary tuberculosis which I analysed,[1] 107 (37%) had a B.S.R. of under 8 mm. in 1 hour. Of the 65 cases with a positive sputum smear stained by the Ziehl–Neelsen method, 17 (26%) had a normal B.S.R.—I am, etc.,

Harrow. H. J. TRENCHARD.

REFERENCE

1 *Lancet*, 1945, **2**, 842.

Treatment of Tuberculous Meningitis

SIR,—With reference to Dr. J. Lorber's criticism (*Journal*, December 26, 1953, p. 1433) of my article (*Journal*, November 21, 1953, p. 1127), I would like to state that this article was intended to be an interim report. The apparent discrepancy between Dr. Lorber's and our analysis of mortality rates is due to the fact that several of the cases who were reported to have died did not die of tuberculous meningitis (see Table III of the article). Of all cases who were reported in the second series, one has since died of tuberculous meningitis, No. 60 remains the same, No. 50 is still paraplegic, and all the others now have a normal C.S.F. and are clinically well, except for two who have a residual weakness of one leg following a hemiplegia. With the exception of case 60, all children of a suitable age are now at school or at nursery school.—I am, etc.,

Durban. WINIFRED C. M. BULKELEY.

The African in Industry

SIR,—The medical needs of the miners in Southern Africa are by no means as "fearful" as Mr. R. Schram (*Journal*, February 6, p. 334) would have us believe. Both the mines and the recruiting organizations provide free medical services to the Africans which are second to none. The health of most Africans is greatly improved during their period of service, since they receive a proper diet with a surfeit of proteins and vitamins which are sadly lacking from their diet at home. In addition, the South African Government provides free medical attention for the Africans and is giving the mission hospitals active financial support in their fight against tuberculosis and other diseases such as malaria, typhoid, bilharzia, drugs for the treatment of which are supplied free. Some areas have already been freed of malaria for several years.

I have had extensive experience in these fields of work, and would suggest to the critics that they bear in mind the vast areas involved and the extremely primitive conditions of African tribal life. The cost of these services has to be borne by a few million Europeans in a country several times the size of England.—I am, etc.,

London, W.C.1. C. C. GRUNBERGER.

The Uvula and East African Negroes

SIR,—I do not think there is any record of the importance which the East African negroes attach to the uvula regarding disease and magic. It is considered by them to be the seat and cause of all diseases affecting the throat and to be the source of all coughs. Therefore they will go to any length and travel enormous distances to find a doctor who will cut their uvula.

My father, during his more than 50 years of practice in Nairobi, 1898–1951, must have cut altogether over 40,000 uvulas. I remember seeing him when I was a boy in the 1920's cut as many as 20 or more a day. He used to do this by the simple method of steadying the patient's head against the wall, catching the uvula with a forceps and snipping it in one stroke with sharp curved scissors. Then he gave the patient some dry ginger to take home and chew. The patient invariably reported that he was cured from his cough and from his sore throat.

The African, particularly of the Jaluo (Lake Victoria area) and the Kikuyu tribe from the Kenya Highlands, is absolutely certain that if his "kilimi" (Swahili word for the uvula) is not cut he will die from his sore throat. He is also convinced that all cough is produced by the "kilimi" and will not hear of any other treatment other than having it cut. The fear of death if "the kilimi is not cut" is probably due to some cases of diphtheria which died and which were diagnosed by the local witch doctor as "kilimi" and helped to establish this cult with the fear of the "kilimi" as the source of all evil to be removed at once. The Kikuyu, particularly the ignorant women from the bush, will insist that the "kilimi" is the sole cause of their child's illness and will refuse to treat the child for bronchopneumonia from which it is really suffering.

Such is the strange belief and cult of the "kilimi" among them, and it is worth putting it on record now, because it will probably disappear with education within the next 25 or 30 years.—I am, etc.,

Nairobi. A. L. RIBEIRO.

Rheumatic Heart Disease Complicating Pregnancy

SIR,—We are grateful to your annotator (*Journal*, January 9, p. 87) and to Drs. Denny and Ryle (*Journal*, January 23, p. 215) for their interest in our article entitled "Rheumatic Heart Disease Complicating Pregnancy" (*Journal*, January 9, p. 70). The suggestion that pregnancy did not contribute to the deaths which occurred later than one year after confinement has been criticized. The relevant facts are these. The average age at death of these women was 38 years. Paul Wood[1] states that the average age at death of cases of mitral stenosis is 35 years. The average age of those who died from heart failure during, or within one year, of pregnancy was 25.4 years. Do these figures suggest that we have indulged in "wishful rather than logical thinking"?

The rejection of therapeutic abortion and sterilization and the references to contraception have also been questioned. Yet the text showed that each patient who died during or within one year of pregnancy was, when first seen, completely unsuitable for artificial termination both by virtue of the stage of pregnancy and of the cardiac condition. Thus no one died because therapeutic abortion was not employed. Since no patient who received antenatal care succumbed, it seems eminently reasonable to argue that antenatal care is preferable to abortion. Four of the women who died from heart failure were primigravidae and the other a gravida 2. If these deaths be used as arguments in favour of sterilization and contraception it would seem to follow that women with heart disease should not be allowed to conceive at all.

Brief reference to the literature shows that we are not alone in believing that pregnancy, if survived, does not contribute to an early demise. Bunim and Rubricius[2] state that "data collected under well controlled conditions" indicate that pregnancy does not alter the course of rheumatic heart disease. Boyer and Hadas[3] found that women who had four or more pregnancies did not die at a younger age than those who had none. Morgan Jones[4] states that "there is no evidence that repeated pregnancies appreciably shorten life." We presume that women who have borne children generally must care for them.

We have seen fatalities result from operative intervention in other centres. Such fatalities frequently escape the obstetrical records, as these procedures are often carried out in gynaecological departments. Scientific analysis of our own cases and of published reports has convinced us that conservative management is the ideal at all stages in all cases of rheumatic heart disease complicating pregnancy. Contrary *facts* have not been published.—We are, etc.,

M. I. DRURY. T. D. HANRATTY.
M. K. O'DRISCOLL. A. P. BARRY.

Dublin.

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2 *Amer. Heart J.*, 1948, 35, 282.
3 *Ann. Intern. Med.*, 1944, 20, 99.
4 *Heart Disease in Pregnancy*, 1951, p. 51. London.

"Antidotarie Chyrurgicall"

SIR,—I was interested to read your note on Banester's *Antidotarie Chyrurgicall* (*Journal*, February 6, p. 329). I have always been puzzled as to the methods by which booksellers and others arrive at their estimate of a book's rarity. It is quite certain that there are more than two other copies of this book in existence, if one is in the Wellcome Museum and the other appeared at a book auction within the last 50 years. There has been a copy in the library of the Royal College of Physicians, Edinburgh, since 1846, which I have before me as I write and which corresponds exactly to the copy you describe.

It is a curious fact, which still awaits explanation, that the Tweed appears to present an insuperable barrier to medical bibliographers. It would take very little time to produce quite an impressive list of medical books of which it has been said that only one or two copies are preserved, and of which another six copies can be found in Scottish libraries. I would add that Banester's book is included in the printed catalogue of this Library, published in 1898.—I am, etc.,

Edinburgh, 2. L. JOLLEY.

SIR,—Your interesting Nova et Vetera "An Extremely Rare Treatise" (*Journal*, February 6, p. 329) assumes too readily that all known copies of John Banester's *Antidotarie Chyrurgicall* of 1589 are recorded in the *Short-Title Catalogue*. The Royal College of Surgeons of England has been fortunate to own a copy of this book since 1818, when it was bequeathed to the College library by William Long, surgeon to St. Bartholomew's Hospital and second Master (President) of the College.—I am, etc.,

London, W.C.2. W. R. LE FANU.

Rh-Hr Nomenclature

SIR,—For some time there has been need for another conference on Rh-Hr nomenclature in order to clarify the confusion which exists among workers in the field. With the appearance of two new books dealing with the Rh-Hr types[1 2] the facts regarding this problem become easily available to anyone. Clearly there is room for only a single nomenclature as in the other blood group systems—namely, the international Rh-Hr nomenclature. It may be, how-

ever, that the people still using the C-D-E notations feel that they should be given a final opportunity to defend their position. In that event they might decide to hold a conference either at the next meeting of the International Society of Haematology in Paris or at the International Congress of Clinical Pathology in Washington. Should it be felt desirable to hold such a meeting, I, for one, would not object, but would instead welcome the opportunity to explain this complex subject again.—I am, etc.,

Brooklyn, N.Y. A. S. WIENER.

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1 Wiener, A. S. (1954). *Rh-Hr Blood Types: Applications in Clinical and Legal Medicine and Anthropology*. Grune and Stratton, N.Y.C.
2 —— (1954). *An Rh-Hr Syllabus: The Types and Their Applications*. Grune and Stratton, N.Y.C.

Rh Antibodies and Domiciliary Midwifery

SIR,—With the establishment of the College of General Practitioners and the re-emergence of the general practitioner I would like to ask for the views of fellow G.P.s about the problem of Rh antibodies in domiciliary midwifery. I would particularly ask those who believe that domiciliary midwifery has distinct advantages over hospital midwifery and those who practise midwifery, not merely to fill in a claim form and pass the buck at any conceivable excuse. With the great strides in the treatment of haemolytic disease, such mental stress caused by the investigation alone is overlooked. The anxiety that can be caused by an "uncomplicated" green card is known only to the woman's G.P. The explanation is often misunderstood and comfort not accepted.

But to come to the specific problem. One is instructed by the local blood transfusion laboratory, and I use the word instructed deliberately, that should a woman have Rh antibodies then she must be confined in hospital. The reason for the instruction is set out with the letter of instruction. I feel that G.P.s are entitled to kick very hard at being instructed, but even if we are to assume that the laboratory's letter is one of advice one has to consider whether their advice is indeed correct and sound.

In the course of the last four years I have had some 300 confinements. All mothers had their blood grouped and there were five cases with Rh antibodies. Of these five, two infants were Rh –ve Coombs –ve, and were of course no problem. Two infants had haemoglobins of 120% approximately, and were very little problem. One infant had a Hb of a little under 100% and required a small transfusion for anaemia on the 8th and 20th day of life. Four of the confinements took place at home and the fifth I reluctantly advised to go into hospital—the advice was even more reluctantly accepted.

Provided one practises within easy reach of a laboratory with 24-hour facilities, and there is a hospital with proper facilities within easy reach, the problem as it appears to me is as follows. The mother has antibodies—the child may or may not have haemolytic disease. Provided one is prepared to be present at the confinement—for clinical assessment of the infant—and provided that one will send a sample of blood to the laboratory for estimation of Hb and Coombs test, what risks are run by a home confinement? Within an hour or two of the child's birth the practitioner will be able to report to the mother. In the great majority of cases this report will be entirely satisfactory. In the small minority of cases it will have been decided that replacement transfusion is required and arrangements will have been made, certainly well within four hours of birth. The case that may possibly require a small transfusion in the second week of life should, of course, not present any immediate problem.

It leaves one with the final small group—which I understand requires immediate transfusion—how extremely rare this group is I do not know. But I am pretty sure that the chances of an individual practitioner meeting a case are small to the extreme. In the past I have allowed my patients with antibodies to be confined at home—I have taken the precautions detailed—and I am very reluctant to give up this practice.

I am sure that many other G.P.s have given this problem thought, and one would be very grateful for their views. For myself, I feel that absolute safety is non-existent. (What about haemolytic disease due to other factors?) And to have given the mother peace of mind and happiness is a very great thing.—I am, etc.,

Gateshead, 8. M. CHALK.

Mongolian Blue Spots

SIR,—Holt[1] describes these spots as follows: "In the skin of the lumbosacral region of the newborn infant one not infrequently finds irregular areas of pale brown or bluish pigmentation, several centimetres in diameter; they may also involve the buttocks and the posterior thoracic wall. These 'Mongolian spots' are quite regularly found in infants of Mongolian race, are fairly frequent in Negroes, but are not uncommon in infants of Caucasian stock. In Negroes they occasionally take the form of decreased, rather than increased, pigmentation. They usually disappear in later infancy or early childhood."

In this country these spots are usually considered to be rare. However, the proportion of foreign blood is steadily increasing, and investigation shows that they are becoming rather more common. During the year 1953 in the maternity wards of a large hospital 778 children were born. Four of them were observed to have Mongolian blue spots (0.51%). These four all had white British fathers. The mother of the first was a Negress and of the second an Indian. The mother of the third was of unknown race as she had herself been adopted in infancy. The parents of the fourth were both English, but the mother's mother was a Jewess from Odessa. An attempt was made to obtain a photograph of one of the spots with panchromatic and infra-red film, but it could not be seen in the prints. A colour photograph was successful.

This experience is recorded, as others may meet with the spots and be puzzled as to their nature. It is important to note that there is no connexion between these spots and Mongoloid idiocy.—I am, etc.,

Bath. H. R. E. WALLIS.

REFERENCE

1 *Holt's Diseases of Infancy and Childhood*, 1933, revised by L. E. Holt and R. McIntosh, 11th ed. New York.

Medicinal Teaspoons

SIR,—Dr. L. Carlyle Lyon's letter (*Journal*, January 23, p. 217) is a timely warning of the possible dangers of inaccurate measuring of medicines. Until comparatively recently most of the medicines supplied to patients for use in their own homes were relatively innocuous even in considerable excess of the correct dose. Now, however, very potent drugs such as methadone, the barbiturates, antihistamines, and sulphonamides are issued as flavoured liquid preparations, especially for administration to children. With these drugs the margin of safety is small, and already at least one child has been poisoned by methadone because of inaccurate measurement of the dose.[1]

There is even greater confusion about the value of a teaspoonful than Dr. Lyon has indicated. In 1947 the British Standards Institute issued a specification for a standard kitchen teaspoonful which holds approximately 49 minims (3 ml.). After protests from the pharmaceutical profession a standard for medicinal teaspoons was introduced in 1949 (B.S.S. 1348, 1949). The requirement for the capacity of this spoon is 60 minims (3.6 ml.) (±5%). In spite of the fact that a fluid drachm has been accepted by the medical, pharmaceutical, and nursing professions for many years as the volume of a teaspoon, at least three values are now in common use by manufacturers. For example, the dose of elixir of piperazine ("antepar") is given as 1 teaspoonful (3.5 ml.), that of chloramphenicol palmitate suspension as 1 teaspoonful (4 ml.), and of benzathine penicillin ("penidural") suspension 1 large teaspoonful (5 ml.).

Marston[2] quotes an example of two preparations of a similar compound being in one case labelled with 3.5 ml. as a teaspoonful and in the other 5 ml. He also mentions another preparation where the following is stated on the same label: "One teaspoonful (5 ml.) three times a day" and then "one drachm (4 ml.) contains x grains, etc." Spalton[3] requested 20 clerical workers in a Leicestershire factory to bring from their homes "one tablespoon and one teaspoon such as you would use to administer medicine." He investigated the capacities of these and found that the teaspoons varied from 2.4 to 7.0 ml. and the tablespoons from 13.4

to 27.2 ml. It is probable that the majority of the public are unaware of the existence of the standard medicinal teaspoon, and the number of homes in which they are to be found must be very small. Surely the time has come to abandon the use of these inaccurate so-called "domestic equivalents" and to advise patients to measure medicines exactly. If drugs were prescribed and dispensed on the metric system it would be quite simple for patients to measure the dose as 4, 5, 10, or 30 ml., etc. Even on the old system it would be better for medicines to be labelled in fluid drachms and ounces and for measures to be supplied.

With modern drugs it is so important that the patient takes the correct dose that accurate medicine measures should be allowed to be prescribed on Health Service prescriptions. Diabetic patients can easily be taught to administer insulin in doses of 1 or 2 ml., and it should not take long to teach others to measure liquid medicines if the appropriate measures are readily available. Finally, it is obviously the duty of doctors and pharmacists to impress on their patients the need for accuracy in measuring medicines and the dangers of overdosage.—I am, etc.,

T. D. WHITTET.

London, W.C.1.

REFERENCES

1 *Pharm. J.*, 1951, **166**, 52.
2 Ibid., 1953, **170**, 387.
3 Ibid., 1949, **162**, 338.

Ophthalmic Waiting-lists

SIR,—The City Surveyor of Birmingham in a recent speech gave a most apt description of a statistician: "A statistician is a man who can draw a straight line from an unfounded assumption to a questionable conclusion." Professor Sorsby in his report on the causes of blindness in England[1] has stated that each year about 2,500 to 3,000 patients are certified blind with cataracts and that some 80% have not had any treatment. Also, some 1,200 to 1,500 are registered blind from glaucoma. The statisticians have therefore jumped to the conclusion that these patients go blind while they are on ophthalmic waiting-lists.

I see, and certify as blind in each year, at least three patients with cataracts who decline operation because of fear (I wonder how many cases our general surgical colleagues see of malignant disease which has advanced to an inoperable stage for the same reason). I see at my hospital clinic at least two patients in each year who present themselves for the first time with grossly constricted visual fields and with optic disks that one could almost "take a bath in." I have no reason to suppose that I am in a different position to any of my colleagues, and I believe the membership roll of the Faculty of Ophthalmologists has 700 or 800 names on it. I have no difficulty, therefore, in accepting these figures. I do not think that any ophthalmic surgeon puts a case of bilateral mature cataracts on a routine waiting-list. I am convinced "glaucoma classes" for opticians would prove more beneficial than "glaucoma clinics" for patients, although the latter seems to me an excellent idea.—I am, etc.,

L. H. G. MOORE.

Dudley.

REFERENCE

1 *The Causes of Blindness in England, 1948-50*, 1953. H.M.S.O., London.

Doctors' Handwriting

SIR,—May I express my utmost sympathy with the views expressed by Dr. Frewen Moor on doctors' handwriting (*Journal*, February 6, p. 334)? Some of my professional friends seem to specialize in forming a totally illegible signature, which seems to me to be almost the worst sin of all, though this is not specifically mentioned by Dr. Moor. It is true that some of them try to mitigate the effect on their correspondents by having a secretary type out the name below the signature, since this by itself affords no clue to identity.

Whatever the reason for execrable writing among doctors, it has to be admitted that it is no recent phenomenon. Dr. Moor's distinguished predecessor in Norwich, Sir Thomas Browne, wrote a terrible hand, and I must admit, as an editor of Browne's *Works*, that I could not have compassed the task without the assistance of a British Museum expert, who first transcribed the MSS. for me so that I might then verify them for myself. Dr. William Harvey is another lamentable example. His writing was so bad that his friend, Sir George Ent, apologized for it in his dedication to the President and Fellows of the College prefixed to Harvey's *De Generatione Animalium*, and explained that he had taken much trouble over the MS. himself, as no one else would have been able to read it. A similar problem now faces the President and Fellows of the College over the transcription of Harvey's remaining unpublished MS.

Some years ago the Marquis of Cholmondeley, aided and abetted by Sir Sydney Cockerell, instituted prizes for handwriting at Eton, Harrow, and Winchester, with the most gratifying results. A generous patron of this kind is perhaps needed for our larger medical schools, though it may be that the prizes should really be awarded among fellows, members, and licentiates of the royal colleges. Indeed, I know several young men recently graduated from my own hospital who have trained themselves as students to write beautiful and legible hands. Perhaps this resolution may falter when they find themselves faced with the exigencies of medical practice—though this does not always happen. The late Sir Norman Moore and his son, Sir Alan Moore, were both famous at St. Bartholomew's for their beautiful handwriting, though it will be urged that neither was afterwards in general practice.

There is one further point. It is not generally realized how many inaccuracies may be traced to the modern demand for everything in typescript. As the author of several bibliographies, books which are useless if inaccurate, I have always written out my material in such a way that it could go straight to the printer without any typewritten intermediary. Typist's errors are thus eliminated, and no printer has yet complained of any difficulty.—I am, etc.,

GEOFFREY KEYNES.

London, W.1.

Hospitals and the Visiting Public

SIR,—We shall be sharing Dr. Doris Odlum's deep concern (*Journal*, February 6, p. 334) over her discovery of the lack of waiting amenities in our hospitals for the relatives of dangerously ill patients. It is our clear duty to ask for conditions calculated to enhearten and comfort rather than accentuate the depression of spirits naturally sorrowful and racked with anxiety. Nothing short of simple consideration in entertaining them is thinkable; and, fortunately, the occasion is likely to evoke sympathetic action by the administrative authorities.—I am, etc.,

A. WILFRID ADAMS.

Bristol, 8.

Cortisone and Manipulation of Knee-joint

SIR,—There are several aspects of the report of the joint committee of the Medical Research Council and the Nuffield Foundation entitled "A Comparison of Cortisone and Codeine Medication as an Adjuvant to Manipulation in Rheumatoid Arthritis" (*Journal*, January 30, p. 233) which invite comment.

(1) The title: this has been wisely reheaded on other pages by you, Sir, as "Cortisone and Manipulation of Knee-joint," as the scope of the investigation was restricted to the knee-joint. The negative result of the knee-joint does not alter the possibility of the value of cortisone cover in manipulating other joints, such as the elbow- and finger-joints where local reactions are marked following manipulation. (2) The opening sentences specify that the essential problem was the flexion deformity of the knees. There are no figures given to indicate whether or not this flexion deformity was improved, and, if so, if there was any difference between the two series. (3) It would appear from the text that no clear distinction was made between manipulations to reduce flexion deformity and manipulations to improve range of movement. The aim influences the technique of manipulation and its after-treatment, and of course the post-manipulative

gain in range. Again, there is no indication as to whether the range of movement recorded is that obtained passively by an observer or that under voluntary control—surely not an unimportant technical point when drugs which might influence performance are being used. (4) It would be interesting to know how the cases were shared between the centres, and whether or not differences were noticed between the results obtained at different centres. (5) As mean values of such a small series of numbers are given then there should be some advantage in including the range of findings or the standard deviations.

I intend no criticism of the actual participants in this trial, but cannot help expressing my surprise at so woolly a report from so eminent a source.—I am, etc.,

Buxton. R. HARRIS.

Displaced Intervertebral Disk

SIR,—Much of the discrepancy of opinion with regard to displaced intervertebral disks has arisen owing to a misunderstanding. There is no evidence that a displaced disk can ever be replaced by means of manipulation. Even when exposed at operation, there are no records of cases in which the surgeon has found it feasible to reduce the prolapsed tissues into their original position. On the other hand, it is undoubtedly true that instances of pain in the back may sometimes be relieved by means of manipulation, but in such cases the symptoms are to be attributed to rheumatic or fibrositic changes in the soft tissues, and not to a displaced disk as is sometimes supposed.

There are thus two distinct conditions of everyday occurrence, the symptoms of which bear a general resemblance to one another but which are of different origin and require different treatment. In cases of displacement of a disk manipulation aggravates the symptoms, whereas immobilization is of benefit. On the other hand, in rheumatic or fibrositic conditions manipulation may be of value, whereas immobilization delays recovery. Fortunately it is not difficult to distinguish between these two conditions, provided that they are approached with an open mind; and it is also fortunate that in both conditions there is a strong tendency for the symptoms to subside, a process aided or impeded according to the treatment employed.—I am, etc.,

Sheffield. R. G. ABERCROMBIE.

Persistent Adult Bed-wetting

SIR,—Even the most Oedipus-ridden of us will welcome Mr. C. Jennings Marshall's paper (*Journal*, February 6, p. 308) not only for its clear statement of the unsolved anatomic and physiological problems of bladder behaviour but for the hope it holds out for those frustrating and intractable adult cases one sees, many of whom are remarkably free from emotional disturbance considering what they have been through. Certain things should be remembered, however, if this paper is not to start, quite unintentionally, a surgical pursuit of enuretics as zealous as that which for a time attached to patients with "disks."

Essential nocturnal enuresis is certainly not a clearly defined entity. In the first place I doubt very much whether even the majority of cases show diurnal precipitancy or frequency. Many patients state that they can sit through cinema performances quite comfortably, and can empty their bladders in as leisurely a way as other people. Secondly, there are children in whom enuresis is one of a number of behaviour disturbances—tempers, destructiveness, spitefulness to a sibling, and so on; and in whom the enuresis disappears with the other things under the impact of a little play therapy. Oedipus or no Oedipus, this just happens to be true. Thirdly, there are deep sleepers, both children and adults, in whom the loss of *cortical* inhibition seems to be the factor. The history is so often striking in that it is related that the patient "dies" when he goes to sleep. If such a patient spends a restful night after 30 mg. of amphetamine, which is what sometimes occurs, there cannot be much doubt about the matter. Lastly, it should be remembered that spontaneous cures occur not only at puberty. There is a continuous falling off in incidence throughout childhood and adolescence.

This leaves a nucleus of cases, which from Mr. Marshall's case reports may be those with "great diurnal precipitancy," in which his theory of the mechanism of enuresis is convincing and his results encouraging. It is good to have Mr. Marshall's reassurance about the nervi erigentes. The stirrings of Nature have a biological function of some importance, and this has usually nothing to do with the Oedipus.—I am, etc.,

London, S.W.1. GERALD GARMANY.

Thiopentone Injection into an Aberrant Artery

SIR,—Dr. M. Swerdlow's presence of mind in leaving the supposedly intravenous needle *in situ* in the aberrant artery until procaine solution had been injected may have saved his patient from serious complications (*Journal*, January 30, p. 258). To avoid this accident two simple precautions are recommended. Careful palpation will reveal pulsation, and the colour of the blood withdrawn will be seen to be bright red if from an artery. It has been stated, however, that blood withdrawn into a syringe containing thiopentone will darken and so nullify this test.

In some experiments carried out for me by Messrs. Abbott Laboratories Ltd. it was found that venous blood drawn into 5% thiopentone solution did darken a little temporarily, but blood taken from an artery into the solution remained bright red. It would appear, therefore, that thiopentone mixed with blood from an artery will not spoil the redness by which entry of an artery might be recognized. In spite of precautions it is possible to enter an artery, and it would be wise always to pause after injecting a little to see if anything untoward is happening.—I am, etc.,

Enfield, Middlesex. C. ALLAN BIRCH.

Galactosaemia

SIR,—The two articles on galactosaemia that appeared in the *Journal* of January 30 (pp. 242 and 245) describing the full investigations done were an admirable contribution to our knowledge of this fascinating disease—probably the only authentic cause of "me milk don't agree with me baby." However, should not a note of caution be sounded, Sir, regarding these blood investigations? These babies are very liable to bleed. We have in hospital now, under the care of Dr. John Apley, a baby with proved galactosaemia who at the age of 14 days was admitted on account of profuse bleeding from the umbilicus that was very difficult to stop. Such haemorrhages are fairly common in this disease. Hence, since the diagnosis of galactosaemia can be confirmed by investigation of the urine alone, venepunctures are better avoided in the early stages of the disease. Should such venepunctures be considered necessary, they should be done with care and confined to the peripheral veins. It seems worth stressing that particularly an internal jugular puncture, or even a femoral puncture, might well prove disastrous.—I am, etc.,

Bristol, 2. BERNARD LAURANCE.

Human Lactation

SIR,—Dr. F. E. Hytten has described (*Journal*, January 23, p. 175) his investigations of milk yield and the content of fat over periods of one day. Although he acknowledges the importance of the draught reflex he has not, it seems, appreciated that the effectiveness of the reflex is not strictly proportional to the fullness of the breast. If the breasts are very full the draught reflex may be exhausted before the breast is emptied and the residual milk be unobtainable. This then doubtless contributes to the available milk at the next feed. Probably, therefore, the diurnal variation in quantity of milk obtained in Dr. Hytten's investigation was produced by the preceding long night interval. Some of the 06.00 hours' unobtainable milk went to increase the 10.00 hours' yield. Dr. Stainer and I,[1] when studying the diurnal

variation in the fat content of milk, took the precaution of emptying the breast at constant intervals and of emptying the breast at the same interval before the outset of each investigation. Under these conditions we found the rate of secretion of milk throughout 24 or even 52 hours to be almost steady. The consistent emptying of the breast gave a clearer picture of the diurnal variation of the fat content because residual milk had been reduced to a minimum.

Although there is reason to believe that milk is modified after leaving the alveolar cell—the passage of globulin direct from plasma,[2] the variation of salt content with fullness of the breast,[3 4] the nature of regression milk and the thinness of the duct epithelium all suggest it—the concept of constant secretion is an important one. Irregular yields indicate difficulties in obtaining milk, failure of draught or failure of suckling technique. They give warning of milk retention and its attendant risk of mastitis. In the management of human lactation they should be viewed as failure of emptying first, because this is common and can so often be remedied.—I am, etc.,

London, W.C.1. MAVIS GUNTHER.

REFERENCES

1 *Lancet*, 1949, 2, 235.
2 Campbell, P. N., *et al.* (1953). *Biochem. J.*, 54, xii.
3 Kermack, W. O., and Miller, R. A. (1951). *Arch. Dis. Childh.*, 26, 265.
4 Gunther, M. (1952). *Brit. J. Nutrit.*, 6, 215.

Piperazine in the Treatment of Threadworms

SIR,—Professor T. Gordonoff (*Journal*, February 13, p. 394) " once gave piperazine by mouth to rats and . . . found it quite toxic. At 4 to 5 g. per kg. there was laboured breathing and twitchings, and some of the animals died." This is a reasonably accurate though not an original observation and agrees in a general way with more detailed tests carried out elsewhere, which were carefully considered before we undertook the trials recorded in our paper (*Journal*, October 3, 1953, p. 755). However, 4 to 5 g. per kg. is more than 60 times the maximum dose we recommend. Many drugs which are freely available to the public would be highly toxic, if not lethal, if given in equivalent quantities—e.g. (in terms of adult dosage), aspirin 2 oz. (62 g.) (180 5-grain (0.32 g.) tablets), santonin or gentian violet 180 gr. (12 g.), quinine 1½ oz. (41 g.), castor oil 1½ pints (0.9 l.). It is perhaps wise to exercise a certain sense of perspective.

Piperazine was commonly used for gout at the beginning of the century, in doses similar to those now recommended for threadworm, without noticeable ill effects. In the last few months it has been widely used in this country as an anthelmintic, with excellent results. The few side-effects which have been reported provide no sound reason for muzzling this very successful treatment.—We are, etc.,

R. H. R. WHITE.
London, N.W.1. O. D. STANDEN.

POINTS FROM LETTERS

Press Publicity

Mr. N. C. WILKINSON (London, W.14) writes: As a journalist who has for some years reported medical news, both as a free-lance and a staff writer, I may say that if doctors are treated with courtesy, their scruples regarding medical professional ethics carefully regarded, and if they are given the chance of verifying that they have been correctly reported before an article or news item is published, then they almost always help the journalist to the fullest extent in their power. This co-operation is a powerful factor in public health education.

Site for Vaccination

Dr. E. P. RIGBY (Nairobi) writes: I am intrigued by the suggestions of Dr. J. Cantor (*Journal*, November 7, 1953, p. 1050) and Dr. Dorothy M. Roels (*Journal*, December 5, 1953, p. 1272). Having at one time had to examine the vaccination scars of landing passengers, I can assure both these doctors that the examination of scars in the sites mentioned by them would cause considerable delay in the clearance of a ship. The most convenient site for this purpose is the volar aspect of the forearm, which, while not being absolutely ideal for cosmetic reasons, is, however, reasonably inconspicuous.

Obituary

WILLIAM DOW, M.D.

Dr. William Dow, formerly medical superintendent of Knightswood Hospital, Glasgow, died on January 31 in his 79th year. Of Highland stock, he was born in Glasgow and received his schooling and medical education in his native city. He graduated M.B., Ch.B. in 1903 and became house-physician to Dr. Finlayson in the Western Infirmary. After a voyage to India he joined the staff of Belvidere Infectious Diseases Hospital, Glasgow, under Dr. John Brownlie—one of the greatest epidemiologists of the day—and at the same time became a member of a coterie of medical men who were all to win distinction in their various fields of medical endeavour. During his stay at Belvidere he wrote a thesis on cerebrospinal meningitis, and for this work was awarded his M.D. degree, with high commendation, in 1908. He was troubled by ill health at this time, and spent the next ten years as medical officer to several extensive sheep ranches in Tierra del Fuego and Patagonia. A wonderful raconteur, he had many interesting stories to tell of his experiences there—of long journeys on horseback, and of meeting and attending to the author and many of the people mentioned in Lucas Bridges's book *Uttermost Part of the Earth*.

In 1919 he returned to Glasgow and after a year in Robroyston Hospital was appointed physician superintendent of Knightswood Infectious Diseases Hospital, where he remained until his retirement in 1940. After only a few months he was recalled to become superintendent of Peel Emergency Hospital, Galashiels, and this post he held till 1947. He then lived quietly in retirement, but maintained an intensive interest in all things medical, and, although greatly crippled by his last illness, was present at a meeting of the Glasgow Medico-Chirurgical Society only a few weeks before his death.

Dow was a kindly and genial man, and was truly beloved by all his residents, whom he affectionately spoke of as his " boys." A clinician of the older school, he had a deep knowledge of infectious diseases and an intuitive and sound clinical judgment. Medically he was rather self-effacing and had a remarkable gift of stimulating the younger members of his staff to original work. In many ways he was the ideal type of physician superintendent, taking a fatherly interest in all his staff—medical and nursing—but also being a firm disciplinarian when occasion demanded it. He was very proud of Knightswood Hospital, and on leaving he provided funds to have a gold medal presented annually to the most proficient nurse. He was a bachelor and is survived by his sister.—P. McK.

We are indebted to Sir ALEXANDER MACGREGOR for the following appreciation: Dr. William Dow was an intimate friend as well as a colleague of mine during most of our professional lives. He was for 20 years physician superintendent of Knightswood Fever Hospital—a hospital which under him and his successor, Dr. Thomas Anderson, acquired a high reputation for clinical and scientific research, which was continuously pursued there throughout the years. Indeed, a post as resident there was much sought after by young graduates in medicine. Dr. Dow had an inquiring mind, and the pursuit of knowledge was one of his main interests in life; above all, he had a gift for communicating

his enthusiasm to his junior staff. It will be a sufficient indication of his qualities and early promise to mention that after graduation he was invited simultaneously by two of the chiefs at the Western Infirmary, including the late Sir William Macewen, to become their resident. His clinical judgment and skill in the diagnosis and treatment of his patients were universally admired and often commented upon. But apart from these qualities he had a flare for administration, so that his hospital was always kept in a state of high efficiency.

Perhaps his most outstanding quality was his genius for friendship. He was by nature warm and friendly; he was that rare person who loves to mingle with young people, and to discuss with them their work and their prospects, and to stimulate them to high endeavour. I know that his memory is revered by almost a generation of former residents, as well as by the nursing and other staff of Knightswood Hospital. When he retired some years ago he was appointed by the Government as medical superintendent of the new War Emergency Hospital at Peel in the Lowlands of Scotland, and it was his duty to organize the hospital from the beginning so as to serve the large area of the border counties—a duty which he performed with the utmost success.

Dr. R. D. SMEDLEY, for 27 years county medical officer of health for West Sussex, died, after a long illness, on January 19 at his home in Goring-by-Sea. He was 77 years of age. Ralph Davies Smedley was born on March 15, 1876, at Pembroke Dock. From Shrewsbury School he went on to Pembroke College, Cambridge, with an exhibition. He completed his medical training at Guy's Hospital, qualifying M.R.C.S., L.R.C.P. in 1902 and graduating M.B. two years later. He took the D.P.H. in 1904 and proceeded to the M.D. degree in 1908. After graduation he returned to Cambridge to undertake research work. Later he became bacteriologist to the City of Leeds, and for five years he was demonstrator of pathology in Sheffield University. His first post in the public health service was in the county of Durham, where he remained until 1913, when he was appointed county medical officer of health for West Sussex. In 1908 he married Dr. Florence Erin Gubb, daughter of Dr. Alfred E. Gubb, who was for long the editor of the *Medical Press and Circular*. His widow and a son and daughter survive him.

Dr. WILLIAM TEMPLETON writes: Dr. R. D. Smedley was virtually the first county medical officer of health for West Sussex, and he at once seized the opportunity of instituting a comprehensive service. He found only two part-time medical officers in the service, doing mainly school work, and within six months he added two whole-time medical officers for tuberculosis and school work, of whom I was one, and three whole-time nurses for staffing school and tuberculosis clinics. Progress was halted by the outbreak of the 1914–18 war, when Dr. Smedley himself, both his whole-time officers, and one of his part-time officers departed on war service. He was fortunate, however, in his wife, who was medically qualified and able to carry on the county health service under war conditions of great difficulty, with the assistance of several part-time temporary officers, though she had her own two young children to look after. In addition, she was appointed inspector of midwives for the county in 1918, and she inaugurated the midwifery and child welfare work under the Maternity and Child Welfare Act of 1918. Early in 1919, on the return of Dr. Smedley and of all his assistants from war service, a new chapter of public health endeavour began. The maternity and child welfare service was extended rapidly, and in 1920 the tuberculosis service became the whole responsibility of the county, and a county sanatorium was essential. After prolonged effort a suitable building was acquired, and Aldingbourne Sanatorium was opened in 1921. Dr. Smedley was from the first the moving spirit in adapting the building and providing equipment, and for many years he was responsible for the administrative work in the institution and grounds. Much of the sanatorium's success was due to his foresight and care. The school medical service also demanded much of Dr. Smedley's time, and the development of treatment, dental, and orthopaedic clinics, and other departments gave full scope to his genius for visualizing the county's needs. He was closely associated with the local voluntary nursing services, which under his guidance became the efficient county nursing service of to-day. Another of his interests was the welfare of the blind. In 1921 he was largely responsible for the formation of the West Sussex Association for the Blind, and was its honorary secretary for many years. The provision of a new county hospital in Chichester was a project with which he was closely concerned, and, with the county architect, he was responsible for much of the planning of a new building opened in 1939. It was put into use immediately as a war hospital and is now the efficient modern general hospital, St. Richard's, Chichester. After a life of exacting responsibility, which from 1920 necessitated almost daily travelling between his home in Worthing and his office in Chichester, he retired in March, 1940. He immediately took an active part in the Home Guard, and served as battalion medical officer. He was a man of great charm and of sound judgment, considerate and thoughtful for all who worked for him, and a real "father" to all his numerous office staff. To his colleagues, not only in his own department but throughout the county, he was always approachable and willing to help and advise.

It was with great sorrow that the Colony of Aden learned of the death on January 7 of Dr. N. R. GUPTA at the Civil Hospital, where he had been in charge of the skin and V.D. departments. Born in Calcutta in 1902, Nirod Ranjan Gupta was the son of the late Dr. Dakshina Ranjan Gupta and Indu Bala das Gupta. He was educated at the Victoria Institution at Singapore, where he won high honours both in scholastic and in athletic fields. He studied medicine at Edinburgh, where he qualified in 1931. On his return to India Dr. Gupta served the Government of Bengal as surgeon-in-charge of the V.D. and skin departments of the Campbell Medical School and Hospital, Calcutta. During the war he served in the Indian Army, attaining the rank of major. In 1945 he joined the staff of the 13th Indian General Hospital at Aden, where he soon found friends at the Civil Hospital, little knowing that later he would become a member of its staff. His last post in India was officer commanding the Indian wing, Combined Military Hospitals, Peshawar. In 1947 he joined the Colonial Medical Service and was posted to the Civil Hospital, Aden, where he soon showed his therapeutic skill in the skin and V.D. departments. He returned to Edinburgh for a year in 1949 in order to take a postgraduate course in his specialty. Dr. Gupta was a loyal and conscientious physician, carrying out his work with exemplary skill. A deeply religious man, he was simple in his habits and charming in manner, and was admired and respected throughout the colony, where he will be sorely missed. He is survived by his wife and three children, to whom we extend our deepest sympathy.—N. H. S.-B.

The death of Surgeon Lieutenant-Commander BASIL GEOGHEGAN, at the early age of 34, is not only a personal tragedy to his many friends, it is a serious loss to the field of research in which he was engaged. His father was the late Dr. Joseph Geoghegan, who practised in Wimpole Street until his death in 1948. Basil Geoghegan was educated at Epsom College and the Middlesex Hospital Medical School, qualifying in 1945. After completing some house appointments, he joined the R.N.V.R. and was transferred to the permanent list of the Royal Navy in November, 1946. For two years he served in H.M.S. *Swift*, and here he was described as an officer of considerable professional ability, and capable and zealous in all his duties. In 1953 he was promoted to the rank of surgeon lieutenant-commander. In December, 1948, Geoghegan was seconded for duty to the Medical Research Council unit for climate and working efficiency in the department of anatomy at Oxford. He was an invaluable member of this unit, for he

combined a flair for sound and accurate research with a quite unusual insight into statistical methods and their practical application. He went on two Arctic cruises in order to carry out investigations on the effect of exposure to cold on naval personnel, and collected a great quantity of valuable data. Much of the latter has still to be analysed (for his illness unfortunately prevented him from preparing all his material for publication), but he established a most interesting relationship between the cholinesterase and vitamin-C content of blood plasma and the environmental temperature, which he communicated in 1952 to the International Congress of Biochemistry in Paris. In a Medical Research Council Report he presented an ingenious mathematical analysis of the cyclical diurnal variations of temperature conditions on board ship. The other data which Geoghegan accumulated on the Arctic cruises have particular reference to the nutritional effects of exposure to cold. In addition to these important observations he made a special study of the determination of body measurements, surface area, and body volume by a photographic technique (published last year in the *American Journal of Physical Anthropology*), and there can be little doubt that this method, from the point of view of its practical application, has many advantages over the traditional methods of anthropometry. Apart from his scientific activities, Geoghegan was a man who knew how to appreciate the good and simple things of life; he was a prodigious reader, and because of his wide interests he was a most engaging conversationalist. He also had a high reputation as a first-class swimmer and frequently took part in inter-university swimming contests. It is a remarkable tribute to his tenacity and loyalty that after his first severe illness in 1951 Geoghegan returned to work and continued to pursue his research with the greatest fortitude until at last, in September last year, the recurrence of the illness finally forced him to give it up.—W. E. Le G. C.

Dr. A. E. ROBERTS, county medical officer of health for Flintshire, died at his home at Rhyl on January 1 at the age of 65. His friends and colleagues will miss him greatly, for his influence permeated well beyond the responsibilities of his post. Aneurin Evan Roberts, who was born in Denbighshire on May 22, 1888, received his medical training at the London Hospital, and graduated M.B., B.S. from London University in 1913. During the first world war he served in the R.A.M.C., and on demobilization in 1919 he was appointed assistant county medical officer in Flintshire. On the death of his predecessor, Dr. A. E. Williams, during the last war, he took over the duties of county medical officer. After the war he attended the D.P.H. course at Liverpool University and obtained the diploma in 1946. In the following year he was appointed county medical officer of Flintshire.

We are indebted to Dr. M. T. ISLWYN JONES for the following appreciation: Having an intimate and detailed knowledge of the county he served, gained over many years, Dr. A. E. Roberts assessed accurately the needs of the community, and his shrewd advice and sound wisdom were greatly appreciated by his colleagues. Youthful in appearance and outlook, he kept abreast of recent developments and trends, while his congenial, energetic, and mature personality powerfully supported new advances. Blessed with the rare gift of true friendship and innate charm, he won the affection and loyalty of all those with whom he came in contact. His fortitude and unwavering acceptance of his illness reflected truly the philosophy which had guided him through life. He continued to work up to within a few days of his death, and received the unstinting support and sympathy of all his staff. He was denied the brief respite which his long years of service had earned, but those who knew him intimately realized that whether in office or not he would have continued to contribute to the betterment of humanity. On January 5 he was buried in the peaceful serenity of Llanrhydd church, near Ruthin, in his native county of Denbigh. Many colleagues and the staff of the Flintshire health department wish to be associated with this tribute to an honoured, valued, and beloved friend. Dr. Roberts leaves a widow, a son, and a daughter, to whom we extend our deepest sympathy.

Dr. LL. S. H. GLANVILLE died at Emsworth, Hampshire, where he had been in practice for over forty years, on January 15 at the age of 75. Llewellyn Stanley Howard Glanville was born on July 25, 1878, and received his medical training at Guy's Hospital, graduating M.B. from London University in 1903. Two years later he obtained the B.S. degree and in 1906 he proceeded to the M.D. He held house appointments at Guy's Hospital, the East London Hospital for Children, and the Samaritan Free Hospital for Women before settling in practice at Emsworth in 1908. Except for the period of his service with the R.A.M.C. in the first world war, he continued in practice at Emsworth until shortly before his death. From 1915 to 1918 he served in Gallipoli, Egypt, and France, and was taken prisoner at St. Quentin in 1918. On return to civilian life he quickly settled down again to his work as a general practitioner, work in which his integrity, acute mind, and keen judgment combined to endear him to his patients and friends. A man of simple tastes and of rather diffident nature, he was nevertheless often asked for help and advice by those in difficulty. His good humour and his friendly chuckle made him a delightful companion. All thoughts of relaxation from work were dispelled in 1939, when retirement or semi-retirement was in his mind, by the outbreak of the second world war, and he remained in full-time practice until 1946, shouldering the burdens left behind by his partners on service in addition to his own duties. After the war his life became quieter and easier, although by no means idle, and he gave valuable assistance as chairman of the house committee of the Victoria Cottage Hospital at Emsworth, to which he was also consulting physician. An example of the very best type of general practitioner, he kept himself abreast of the many advances in medical treatment. He was happy in his work and never spared himself; he had, therefore, the affection of all his patients, to whom he was both kind and generous. For recreation he would take walks over the South Downs, or sail in Chichester harbour, or tend his beautiful garden. His life was saddened in 1951 by the death of his wife, whom he had nursed devotedly during her last illness.

Dr. C. D. EDWARDS died on January 15 at Kington, Herefordshire, at the age of 84. The son of the late Edwin Evans Edwards, Charles Derwent Edwards was born at Rugeley, Staffs, in 1870, and was educated at Hereford Cathedral School, St. John's College, Cambridge, and Guy's Hospital. After graduating M.B., B.Ch. in 1896, he held resident posts at his teaching hospital, and then went into practice, first at Woodford, Essex, and later at Chalford, Gloucestershire. In 1910 he proceeded to the degree of M.D., and in the following year he took the D.P.H. During the first world war he served in the R.A.M.C. with the rank of captain, and he was sanitary specialist to the 34th Division and medical officer of the 102nd Field Ambulance. He was awarded the Military Cross for his services. After his retirement he lived at Kington, and took an important part in the life of the district, as can be seen from the following description of his interests and activities. He was particularly devoted to the parish church, of which he was churchwarden, and he did a great deal for the maintenance of the church itself, and was largely responsible for the building of the Huntington Parish Hall. He was in fact a generous supporter of many charities. Chairman of the Huntington Parish Council for many years, he was also for some time a member of the Kington Rural District Council. He was always concerned in the assistance of disabled men, and worked unceasingly for the British Legion, being chairman of the Kington Branch from 1927 to 1953. A vice-president of the North Hereford Conservative Association and chairman of the Huntington Branch, he was also chairman of the Leominster Division of the Junior Imperial League. One of his appointments was that of Commissioner of In-

come Tax. As a member of the committee and a trustee of the Victoria Cottage Hospital, Kington, he was a considerable benefactor, and he was chairman of the Kington District Nursing Association, as well as being a member of the executive committee of the County Nursing Association. Interested as he was in helping young people, he was a keen supporter of the Boy Scouts Association, of which he was a district commissioner, a governor of the Lady Hawkins Grammar School, and chairman and correspondent of the managers of Mahollam School. Local agriculture also benefited by his enthusiasm : he was a member of the National Farmers' Union and of the Kington Local Committee of the Herefordshire War Agricultural Committee, and president of the Kington Young Farmers' Club since its foundation. For many years chairman of the Kington Horse Show and Agricultural Society, he helped greatly to build it up. He was particularly successful as a rose grower, and was also a keen bee-keeper, winning many prizes for his honey. A fine sportsman, he played Rugby football while at Cambridge and represented the university in athletics. He greatly enjoyed hunting and shooting, and was an ardent fisherman, being chairman and later president of the Kington Fishing Club. Another of his interests was first-aid work, and he was associated with both the British Red Cross Society and the St. John Ambulance Brigade, being president of the Kington Division of the latter. In 1898 he married Janet Louise Paterson, at one time a sister at Guy's Hospital : she died in 1949. Dr. Edwards will be missed by everyone with whom he came in contact. —W. L. J.

DR. CHARLES HERBERT GOULDSMITH PRANCE died at Woodford Green on January 21 at the age of 84. He was a medical student at St. Bartholomew's Hospital and qualified in 1897. He practised in turn at Polyphant, near Launceston, at Plympton, South Devon, and then in Cornwall again, this time at St. Austell. During the first world war he served in the R.A.M.C. and was present at the Gallipoli landings. He attained the rank of major and was mentioned in dispatches for his services. After demobilization he settled at Ashtead, in Surrey, where he was in practice until he retired in 1940. He then became chairman of a medical board. At Ashtead he served on the welfare committee of the local branch of the British Legion for many years, being chairman of the branch in 1936. In 1945 he went to live at Mentone, in the South of France, but he returned to England shortly before his death. In the days when Dr. Prance first entered general practice great demands were made on the family doctor, who, besides being physician, general surgeon, and accoucheur, might be called upon to act as dental surgeon, dental mechanic, or veterinary surgeon : with his resourcefulness and versatility, however, Dr. Prance was capable of dealing with any emergency. His unbounded energy and his great love and understanding of his fellow-men endeared him to all who knew him.—S. F. H.

DR. NOEL KEMM died suddenly at Bristol on January 23 at the age of 60. Noel Edward ffarnewell Kemm, who was born on November 24, 1893, came of a medical family, both his grandfather and father having been in practice in the West Country, and his brother being in practice at Cheddar. He was educated at Blundells School, and from there went on to Bristol University as a medical student. Immediately after qualification, in 1918, he entered the R.A.M.C. and saw active service in Palestine as medical officer to the Queen's Bays. After demobilization he held a number of appointments at Bristol Royal Infirmary and then went to the Richard Murray Hospital, Blackhill, County Durham, as resident medical officer for three years. Returning to Bristol as surgical registrar at the Royal Infirmary, he obtained the London degrees of M.B., B.S. and the F.R.C.S.Ed. in 1925. Eventually he settled in practice at Clifton, but after a time he became interested in occupational health, and for the last 10 years had acted as whole-time industrial medical officer. During the last war he served as a combatant officer in a Bristol Home Guard infantry battalion. Dr. Kemm had many interests outside his profession, and his tall, sparse figure was well known and welcomed at meetings of local medical societies and at social functions. His bluff manner could never conceal his great kindness of heart, and he was a staunch friend to many. He continued to work, as he wished, to the end. He is survived by a widow and stepdaughter, to whom our deepest sympathy is extended.—R. B. B.

DR. C. P. DONNISON, consulting physician to the children's department of the Cheltenham General Hospital, died at his home at Cheltenham on January 23 after a short illness. Cyril Percy Donnison served as a pilot in the Royal Flying Corps during the first world war, and then began the study of medicine at the London Hospital, qualifying M.R.C.S., L.R.C.P. in 1924. Having joined the Colonial Medical Service, he worked for the next three years in Kenya. The results of his careful observations of the health of Africans were incorporated in his book *Civilization and Disease*, published in 1937. On returning to England, he entered general practice and took the London degrees of M.B., B.S. in 1928. Two years later he proceeded to the M.D., and in 1934 took the M.R.C.P. He practised at first at Benfleet and later moved to Cheltenham, where his interest in children led to his appointment as paediatrician to the Cheltenham and County Child Guidance Clinic and afterwards as consulting physician to the children's department of Cheltenham General Hospital. He was also a member of the medical staff of the two well-known public schools in Cheltenham. With the advent of the National Health Service he gave up general practice and worked purely as a consulting paediatrician. When he was in general practice he maintained a very high standard of work, himself carrying out such clinical pathology as was required, and he brought to consulting practice the same painstaking care over every detail. This, supported by an extensive knowledge of the literature of his specialty, gave his opinion a value which was greatly appreciated by doctors who sought his help. His other great interest, apart from his work, was sailing, and it was characteristic of him that he should bring to his hobby the same scrupulous care that he brought to his work. His death, at the comparatively early age of 55, has removed a friend and a colleague who was greatly loved and respected. He leaves a widow and two daughters, both of whom are working in hospitals—one as a house-physician and the other as an almoner.—R. G. A.

DR. H. S. GABB, a member of a well-known Hastings family and consulting surgeon to the Royal East Sussex Hospital, died suddenly at his home at Hastings on January 24 at the age of 76. Harry Secretan Gabb was born at Framlingham, Suffolk, on November 16, 1877, and was educated at Walsall Grammar School, Wellington College, Shropshire, and Shrewsbury School. Entering Downing College, Cambridge, in 1895 with an open scholarship in natural science and a scholarship from the Shropshire County Council, he obtained the B.A. degree with a first class in the Natural Sciences Tripos in 1898. He then went to Charing Cross Hospital Medical School with a university scholarship and took the M.B., B.Chir. degrees in 1901. At hospital he won the Llewellyn scholarship, and, after holding house appointments there and at the Central London Ophthalmic Hospital, he became senior house-surgeon at the South Devon and East Cornwall Hospital, Plymouth. In 1904 he joined his cousin, the late Dr. C. B. Gabb, in practice at Hastings, where he soon gained the affection of his patients, who regarded him as family physician and friend, and of his professional colleagues. He combined the work of his private practice with the duties of a surgeon at the Royal East Sussex Hospital, and in 1948 he became consulting surgeon to the hospital. During the first world war he was in the R.A.M.C. and saw service in France. He represented the Hastings Division of the British Medical Association at the Annual Representative Meetings in 1944, when the proposals for a National Health Service were debated, and in 1945. Dr. Gabb held decided views about the Service, which he never entered. He was president of

the East Sussex Medico-Chirurgical Society on two occasions. For 25 years chairman of the Hastings division of the St. John Ambulance Association, he was appointed a Serving Brother of the Order of St. John of Jerusalem for his work in that connexion. From the time he first settled at Hastings he was an enthusiastic member of the local rowing club and was its vice-president for many years; earlier, while at Cambridge, he had rowed stroke in the first college boat. He was president of the Downing College Association in 1952. He married Melita, daughter of the late Lieutenant-Colonel J. W. Belcher, A.M.S., in 1905, and there were six sons—two of whom are now members of the medical profession—and three daughters of the marriage. The presence of one, sometimes two, of his sons each year at Tonbridge School over a period of 20 years was a notable record for the members of one family.

Dr. CHARLES ROBERTSON, who died at his home at Bonnyrigg, Midlothian, on January 27 at the age of 70, was a well-known rifle shot. He was born in India on November 17, 1883, the son of an officer in the Indian Medical Service, and from Madras University, where he took the B.A. in 1901, he entered Edinburgh University as a medical student, obtaining the M.B., Ch.B. degrees in 1907. He proceeded to the M.D. in 1917. After graduating in medicine he held house appointments at the Gloucestershire Royal Infirmary, the Rotherham Hospital and Dispensary, and the Horton County Mental Hospital. He then settled in practice at Bonnyrigg, where he served a wide community in the Esk Valley district. During the first world war he served as a captain in the R.A.M.C. After his retirement from active practice in 1951 he went on a visit to India, where his mother still lived. For many years of his life rifle-shooting was an absorbing interest and he became an expert marksman. He shot at Bisley for the Elcho Shield about 12 times, for the Kolhapur Imperial Challenge Cup in 1935, when he represented India, and for the King's Prize in 1939, when he reached the final stage of the competition. At Cambuslang he twice won the championship of the Scottish Rifle Association. Cricket, too, claimed his support whenever opportunity arose, his play at one time reaching first-class standard. He married Miss Winnifred N. Kirkwood in 1913 and had one son and two daughters. His son, a squadron leader in the R.A.F., was killed in an air crash in 1948, and Mrs. Robertson also predeceased him.

With the death of Dr. P. F. TINNE, at the age of 79 years on January 28, the profession in Liverpool has lost one of its most senior and best-loved general-practitioner members. Philip Frederic Tinne was the eldest son of Ernest Tinne, head of the firm of Sandbach Tinne and Company, shipowners and merchants of Liverpool. From Eton he went on to Magdalen College, Oxford, and rowed in the college boat in 1898. He continued his medical studies at St. George's Hospital, where he later held the post of casualty officer, after qualifying in 1902. Shortly afterwards he graduated B.M., B.Ch. at Oxford. A period as ship surgeon with the Elder Dempster Line followed, after which he returned to Liverpool to practise in Garston, Grassendale, and Aigburth for more than half a century. He served on the staff of the Garston Hospital for the greater part of his professional life and saw it develop from a small cottage hospital, occupying two adjoining houses, to a busy general hospital of modern design, serving an ever-expanding industrial community. At no time was his devotion to the hospital seen to better advantage than during the air bombardments of 1940 and 1941. The hospital was then a casualty clearing station, of which he was in charge, and, though no longer young, he was never missing from the post of duty. Night after night when the sirens sounded he was to be seen trudging the mile or so which lay between his home and the hospital, apparently oblivious of the hail of metal falling from the anti-aircraft barrage and ready, after a busy day, to meet the arduous and often harrowing experiences of the night. He was the trusted medical adviser of successive generations of his patients, and maintained in exemplary fashion the high traditions of the English family doctor. He delighted in the society of his colleagues. He joined the Liverpool Medical Institution in 1905, was a member of its council in 1917, and was warmly congratulated at an enthusiastic meeting of the members when he attained life membership in 1950. Though medicine was his first love, his interests were wide and lay particularly in the sphere of natural history. He was president of the Liverpool Microscopical Society on ten occasions. He wrote well and was the author of several short stories. He was a staunch member of Aigburth Parish Church, of which he was a churchwarden for the last ten years of his life. The head of a devoted and united family, he is survived by his widow, four daughters, and two sons, one of whom is also a doctor.

Dr. W. F. HAMILTON writes: Mr. DAVID LIGAT (whose obituary notice was published in the *Journal* of February 6, p. 338), of St. Leonards-on-Sea, died young in spite of his 80 years, young in spirit, in mentality, and in appearance. I had known him for almost 30 years, and had always wondered if enthusiasm were the secret of perpetual youth or if his extreme youthfulness were the source of his abundant enthusiasm. For enthusiasm, courage, honesty, and tenacity of purpose were the keynotes of his character, and kindliness and almost boyish cheerfulness the grace-notes. This enthusiasm was shown in all his activities—his music, his golf, and above all his surgery. But here he never let it interfere with his judgment or allowed it to lead him into an operation which he did not honestly believe was for the good of his patient. News of the courage he displayed when severely injured by enemy action filtered out to me in Italy, and this same courage sustained him through the many months of pain which followed and with his cheerfulness and tenacity enabled him to triumph over the disaster of the loss of his right arm. Deprived of all active participation in professional work and his former recreations, he took up bowls, and, though the lack of his arm made balance in this game difficult, he persisted and largely overcame this handicap. Faced with the difficulty of writing easily and legibly with his left hand, he learned to type. When I saw him a few weeks ago, though already confined to bed by his fatal illness, he was still keenly interested in medical progress and in the affairs of the world. He discussed articles very recently published in the journals and described in vivid language a tour he had made to Ceylon a short time previously. At the recollection of some amusing incident his ever-youthful laugh would ring out, perhaps not so strongly as before, but with all its old gaiety. To Mrs. Ligat, who was his constant companion for so many years and who shared his joy and skill in music, and to their daughter the deep sympathy of their many friends will be extended.

Dr. JAMES SOMERVILLE MCLESTER, a former president of the American Medical Association, died at Birmingham, Alabama, on February 7, aged 77. He was born at Tuscaloosa, Alabama, on January 25, 1877, and began his medical education at the University of Alabama. After graduating at the University of Virginia in 1899, he visited clinics at Göttingen, Freiburg, and other university cities in Europe. On his return home he was appointed professor of pathology at Birmingham Medical College in 1902. Soon afterwards his title was changed to professor of medicine, and he held this post until 1912. In 1919 he was appointed professor of medicine at the newly established school of the medical sciences, University of Alabama, becoming professor emeritus in 1949. During the first world war he was consultant in medicine to the American Expeditionary Forces, and in the last war he was chairman of the subcommittee of the National Research Council which was responsible for planning diets for the American services. During his many years of work for the American Medical Association he filled several important offices, including the chairmanship of the Council on Food and Nutrition. He was president of the Association in 1935. McLester's scientific work centred chiefly on metabolic and nutritional disorders, and he made many important contributions to the literature on the subject.

Medical Notes in Parliament

SMOKING AND LUNG CANCER

The MINISTER OF HEALTH made a statement in a Parliamentary written reply on February 12 on smoking and cancer of the lung, having received the advice of the Standing Advisory Committee on Cancer and Radiotherapy. Mr. Iain Macleod said: "I accept the committee's view that the statistical evidence points to smoking as a factor in lung cancer, but I would draw attention to the fact that there is so far no firm evidence of the way in which smoking may cause lung cancer or of the extent to which it does so. Research into the causes of lung cancer has been pressed forward by the Government and by other agencies in view of the increase in the incidence of this disease, and we must look to the results of its vigorous pursuit to determine future action."

He also told the House that before these recommendations were considered by the Government the tobacco companies had offered to give £250,000 for research. They had, on his advice, agreed to offer this money to the Medical Research Council.

Mr. Macleod said that the standing advisory committee had had this matter under consideration for three years. As a result of preliminary investigations a panel under the chairmanship of the Government Actuary was set up in 1953 to inquire and report. He had now been advised by the committee in the following terms:

"Having considered the report of the panel under the chairmanship of the Government Actuary on the statistical evidence of an association between smoking and cancer of the lung, and having reviewed the other evidence available to them, the committee are of opinion:

"(1) It must be regarded as established that there is a relationship between smoking and cancer of the lung.

"(2) Though there is a strong presumption that the relationship is causal, there is evidence that the relationship is not a simple one, since

"(*a*) the evidence in support of the presence in tobacco smoke of a carcinogenic agent causing cancer of the lung is not yet certain;

"(*b*) the statistical evidence indicates that it is unlikely that the increase in the incidence of cancer of the lung is due entirely to increases in smoking;

"(*c*) the difference in incidence between urban and rural areas and between different towns suggests that other factors may be operating—for example, atmospheric pollution, occupational risks.

"(3) Although no immediate dramatic fall in death rates could be expected if smoking ceased, since the development of lung cancer may be the result of factors operating over many years, and although no reliable quantitative estimates can be made of the effect of smoking on the incidence of cancer of the lung, it is desirable that young people should be warned of the risks apparently attendant on excessive smoking. It would appear that the risk increases with the amount smoked, particularly of cigarettes."

Assistants and Partnerships

Mr. T. HUBBARD asked the Secretary of State for Scotland on February 9 if he was aware that when medical practitioners worked in partnership patients might enter the name of one of the partners as their doctor for Health Service purposes; that this partner might thus accumulate more names on his register than was provided for in the regulations, although the patients were aware that they might be attended by another partner; and if he would take action to ensure that no physician in partnership with colleagues was refused payment in such circumstances.

Commander T. D. GALBRAITH, Under Secretary for Scotland, said that a doctor in partnership had certain personal obligations to patients on his own list. By limiting the size of the list the regulations sought to prevent the acceptance of patients towards whom these obligations could not in practice be discharged. The arrangements had been settled in agreement with the representatives of the profession, and he saw no reason to alter them.

Mr. HUBBARD argued that one of the results of the arrangement was that doctors who might wish to take assistants into partnership held back, because they would have to canvass their patients in order to have them transferred to the name of the new partner. Many men who might well have become partners were consequently still assistants. Commander GALBRAITH replied that the arrangements allowed the doctor to have 4,500 patients on his list so long as the average throughout the practice was 3,500. He did not see how a doctor could reasonably be expected to look after more than 4,500 patients. Mr. HUBBARD said that was not the point. Where a doctor had an assistant, the number of patients was equally divided between them, but when the assistant was promoted to a partnership there was a new arrangement, and, unless the patients nominated the partner, the doctor did not find the patients equally allocated. For that reason the regulations required some alteration so that some encouragement was given to doctors to promote assistants to be partners.

Dollars for Heart Specialists

Mr. EDWARD SHORT asked the Chancellor of the Exchequer on February 11 on what grounds dollar allowances had been refused to 14 British heart specialists who wished to attend the World Congress in Cardiology in Washington. Mr. REGINALD MAUDLING, Economic Secretary to the Treasury, replied that dollar expenditure had to be watched very carefully in this as in other fields. He was, however, arranging for this case to be reconsidered.

Calomel Referred to Poisons Board

Mr. S. SWINGLER asked the Home Secretary on February 11 if, in view of the dangers of mercury poisoning disclosed at recent inquests, he would now put calomel on Schedule 1 of the Poisons List. Sir DAVID MAXWELL FYFE said that he was referring the suggestion to the Poisons Board.

Medical Gases Inquiry

Mr. PETER THORNEYCROFT, President of the Board of Trade, informed the House of Commons on February 9 that on February 1 he had referred to the Monopolies Commission the supply of certain industrial and medical gases—namely, oxygen, dissolved acetylene, and propane.

The commission will investigate and report on whether the conditions to which the Monopolies Act applies prevail, and whether the conditions or any of the things done operate against the public interest or may be expected to do so.

Toxic Substances in Food Production

Sir THOMAS DUGDALE, Minister of Agriculture, announcing the Government's general acceptance of the recommendations in the second report of the working party on the use of toxic chemicals in agriculture, stated on February 9 that an interdepartmental committee was to be set up to keep under constant review all risks that might arise from the use of toxic substances in food production and storage, and to make recommendations to the Ministers concerned. Professor Zuckerman, who was chairman of the working party, had agreed to accept appointment as the independent chairman of the committee for an initial period.

Sir Thomas Dugdale said the Zuckerman report dealt with residues in food and possible risks to the consumer. The use of these substances played an important part in food production, and it was encouraging that there was no evidence of adverse effects resulting from current practices; but the position must clearly be kept under close review.

Preliminary discussions with the Association of British Insecticide Manufacturers suggested that, subject to safeguards to avoid premature disclosure, it should be possible to arrange for their members to notify proposals for new toxic substances or for new uses of existing substances which involved toxic hazards. It was hoped and expected that these and similar voluntary arrangements would obviate the

need for any statutory requirement of notification. The Government was considering, in consultation with the interests concerned, the suggestion that the use of bacterial rodenticides should be discontinued in view of possible risks to public health. These preparations, which were not on sale to the general public, had been in use on a considerable scale for many years. The companies using them had agreed to adopt, with minor modifications, the precautions recommended in the report, the chief of which were already part of their current practice. They had also offered to collaborate with the appropriate Departments, who would keep the matter under close review.

Disability in the Ageing

Dr. HORACE KING, pressing the case for a speedy revision of the supplementary allowances for disabled ex-Service men, said in the House of Commons on February 8 that not only had the real value of the basic pension declined but disability got worse with old age. A group of M.P.s had been urging the Minister to give extra pensions for the ageing limbless. He hoped the Minister would not say that they must wait until the Rock Carling Committee's report had been received and fully considered. It did not need a medical report to tell them that physical handicaps were more burdensome in old age.

The Ministry had always been advised by medical men, and properly so. But medical men must give a medical opinion; if a disabled man's condition deteriorated the medical men must state what was the scientific truth—that if one lost one leg the other did not tend to degenerate. If a doctor gave false medical testimony he would cause much greater general anxiety than the extra pension would give relief to a particular man. But this was a human problem, not a medical one, and a man who had lost a leg in the war and then lost another ought to receive 100% disability pension, whatever the doctors said.

Brigadier J. G. SMYTH, Parliamentary Secretary, Ministry of Pensions, said the work of the Rock Carling Committee had taken longer than had been expected, but it must be done with the greatest thoroughness, because its findings would be of supreme importance. They would all hope that the result of the committee's work would indicate that amputees were not more liable to cardiovascular disorders than other people, and that their expectation of life was in no way reduced. But if the evidence was to the contrary they would have to re-examine the whole problem. On present medical evidence there was no reason to regard the disabled amputee as being any different from all the other classes of disabled. Dr. King had suggested that the Minister should disregard his medical experts in certain cases. In accordance with the royal warrant the Minister must abide by the decision of his medical advisers in purely medical cases, except where some serious medical doubt was disclosed by the evidence, when the Minister could appoint an independent medical expert; and in addition to that there were the tribunals.

Anaesthesia on Animals

The Protection of Animals (Anaesthetics) Bill was given a second reading in the House of Commons on February 12. Its purpose is to bring up to date the law on the use of anaesthetics in animal operations, and Viscountess DAVIDSON, who introduced the Bill, said there had been no legislation on the subject since the original Act of 1919, which the veterinary profession considered now to be too limited and rigid. The Bill made the use of anaesthetics compulsory for all except minor operations on animals, but not on birds, fish, or reptiles. It would give the veterinary profession a better opportunity in the application of modern scientific developments in anaesthesia. The motion was seconded by Mr. SOMERVILLE HASTINGS, who said the object of operations on animals was for the benefit of human beings. For that reason it behoved them to carry out operative treatment with as little discomfort to the animals as could be managed. That was the aim of the Bill. Surgery in animals and in humans had much in common, and had changed materially since 1919.

The Bill received Government support from Mr. G. R. H. NUGENT, Parliamentary Secretary to the Ministry of Agriculture. Sir THOMAS MOORE described it as a half-way house between those who believed that vivisection was a necessity and the antivivisectionists.

Fees for Inquest Work

The Coroners Bill, which enables the Home Secretary to prescribe the fees and allowances payable to witnesses at coroners' inquests and to medical practitioners who make post-mortem examinations for coroners, was given a second reading in the House of Commons on February 12. Sir HUGH LUCAS-TOOTH, Under Secretary, Home Office, promised Government assistance in the further stages of the Bill. During the short debate Dr. A. D. D. BROUGHTON said that the Bill was long overdue. He had conducted many post-mortem examinations; they occupied much time, and the fees were inadequate.

New Abortion Bill.—Lord Amulree introduced in the House of Lords on January 26 a private Member's Bill to amend s. 58 of the Offences against the Person Act, 1861.

Medico-Legal

PRINCIPLES OF CRIMINAL LAW

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

Textbooks on the criminal law are inclined to approach the subject as a series of rules relating to particular crimes and groups of crimes. In *Criminal Law*[1] Professor Glanville Williams approaches the subject by analysing and expounding the principles which underlie the rules and are common to most if not all crimes. Later, the author says in his preface, he hopes to follow it with a companion volume on specific crimes.

Anyone seriously interested in the criminal law will find the book of great interest. It is not a practitioner's textbook but a penetrating exploration of the foundations, the superstructure of which is to be seen in the everyday administration of justice. Those concerned in the administration of criminal justice will, if they approach the argument with the concentration it deserves, find much to stimulate their thought.

Doctors in particular will find in the chapter on mental abnormality a profound and comprehensive examination not only of the M'Naghten Rules but of the machinery for dealing with the mentally abnormal in the courts of summary jurisdiction. Though this attracts less popular attention, it is of no less importance to the community. When the next Straffen shocks doctors and lawyers into argument on the M'Naghten Rules, they would do well to read this chapter before taking up their pens to write to the press. Anyone interested in the why of the criminal law as well as in the how and the what will find their work repaid if they read this book.

[1] *Criminal Law: The General Part.* By Glanville L. Williams, LL.D. (Pp. 736. £3 3s.) London: Stevens and Sons Ltd. 1953.

Universities and Colleges

UNIVERSITY OF OXFORD

In a Congregation held on December 12, 1953, the following degrees were conferred:

B.M.—N. L. Gittleson, T. H. Hughes-Davies, R. T. Wood, R. H. O. Parker, C. A. S. Wink, J. D. Craven, M. G. Gelder, J. Mould, I. Hadfield, R. C. Ilbert, B. E. Juel-Jensen, S. Solomons, C. E. Strode, J. E. Cooper, C. T. Howe, J. D. Wigdahl, R. F. N. Duke, V. D. Pippett, S. E. Smith, G. H. Bush, C. R. Tribe, J. Bradshaw, M. C. ffrench-Constant, J. M. Jones, G. L. Asherson, G. St. John-Ives, D. K. Croll, G. Bennett, Barbara H. MacGibbon, Mrs. Hassia Orgel, Brenda L. Radford, Muriel K. Quick, Eileen B. B. Young, Mrs. Ann G. Parker, and (in absence) M. C. Brain.

UNIVERSITY OF CAMBRIDGE

Drs. B. Towers and A. D. Dickson have been appointed University Demonstrators in the Department of Anatomy with tenure for three years from April 1, 1954, and October 1, 1954, respectively.

In Congregation on December 12, 1953, the degree of M.B. was conferred, by proxy, on John Hughes.

UNIVERSITY OF DURHAM

The following medical degrees were conferred in Congregation on December 19, 1953:

M.B., B.S.—C. R. B. Bamford, R. W. Barker, J. A. Bewick, R. Brown, A. R. Buchan, B. Colville, J. P. Dawson, W. I. Hay, D. W. B. Hogg, Margaret R. Hutton, R. Jackson, R. F. Laverick, C. M. Leon, T. M. McKenzie, C. Madhoo, J. N. O'Neill, S. D. Pagden, A. Petterson, Madeleine A. Sharp, S. G. Shaw, Jane Sherman, A. J. Talbutt, A. A. Walker, *P. L. Campbell, *W. B. Chambers.

In absentia.

UNIVERSITY OF WALES

The following candidates at the Welsh National School of Medicine have satisfied the examiners at the examination indicated:

D.P.H.—R. B. Davies, R. G. Evans, Anita J. Thomas.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examinations indicated:

M.D.—June P. Arnold, L. Mandel.

M.CH.ORTH.—J. C. Anderson, M. Anwer, J. M. Gold, J. Harari, T. J. Mills, R. Owen, F. W. Shea, G. A. Wetherell.

CH.M.—P. A. P. Joseph, J. K. M. Rawlinson, J. T. Rowling, and S. E. Wijetilaka have satisfied the examiners in the clinical and oral sections of the examination.

M.B., CH.B.—Margaret J. Alltree, S. J. Alltree, D. R. Cole, T. R. W. Cowell, R. H. Cranmer-Gordon, B. E. Dalton, L. M. Ellis, M. A. R. Eslick, C. D. Fisher, Pamela M. Frazer, D. N. Guest, F. Hewitt, C. D. James, I. V. Lishman, D. R. Morris, S. Naylor, N. N. Nehra, D. F. Rice, A. M. Stewart. *Passed in separate subjects:* N. McKie (surgery and obstetrics and gynaecology), Pear Ramkallop (medicine and obstetrics and gynaecology), A. Swithinbank (medicine and surgery). *Part III:* T. R. Evans, T. R. T. Hughes, J. B. Middleton, B. J. O'Dowd.

DIPLOMA IN PUBLIC HEALTH.—Part I: Ursula M. Anderson, G. T. Crook, Jeannette Diamond, A. W. Iljon, Joan Knowles, P. Lorigan, H. P. P. Morris, D. S. Parken, J. L. Patterson, Joyce K. Watkin.

CERTIFICATE IN PUBLIC HEALTH.—Margaret Hughes, Eira Thomas.

DIPLOMA IN RADIOLOGY (RADIO-DIAGNOSIS).—J. G. Kay.

UNIVERSITY OF SHEFFIELD

The following appointments were made on December 18, 1953: Dr. J. D. S. Hammond, Full-time Research Assistant in Medicine; Dr. C. C. Bowley, Part-time Honorary Lecturer in Pathology; Dr. H. L. J. Wilson, Part-time Instructor in Anaesthetics.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The following candidates have been awarded the Diploma in Obstetrics: C. A. C. Abraham, R. D. Allen, J. P. Alvey, A. G. Amias, J. A. D. Anderson, J. R. Angwin, J. H. Armstrong, R. Bain, D. A. Baird, Doreen S. Ball, G. V. Balmforth, J. A. C. Bamford, A. A. Bapty, A. P. Barclay, N. H. Barley, H. C. Barr, A. C. Beatty, H. R. C. Benny, W. G. Benson, J. S. Berkeley, Margaret S. Beverland, J. R. Billinghurst, Dorothy G. Blackett-Ord, R. C. Bloomfield, D. G. Bluett, Audrey A. Boutwood, Iona M. Brereton, R. W. Brotherwood, B. J. Brown, C. T. Brown, G. L. Brown, J. D. Bruce, C. V. Bullen, A. K. Burt, Seonaid C. Cameron, Patricia E. Campbell, R. W. Campbell, R. Carr, Sumathi R. Chandy, Sin Giap Chua, B. W. Cole, P. F. A. Crawshaw, Barbara M. St. J. Coventry, H. J. E. Cox, G. E. Crawford, P. M. Crawford, Flora M. Dale, G. M. Davidson, I. F. Digby, Josephine Dolan, K. C. Easton, Barbara C. Edwards, B. D. Ellis, Doreen A. Ellis, L. Elton, H. A. Evans, Margaret G. Fairman, D. C. Faull, L. C. Fernandez, F. I. Firth, J. A. Fleming, Marjorie H. E. Flowerday, D. S. Foster, I. H. Gardner, W. A. Gentle, W. J. Glover, M. Goodman, Leonora H. Goulty, C. W. Grant, Monica C. Grant, C. C. Griffiths, Jean M. Halliwell, Elinor C. Hamlin, J. L. Hanington, Maureen E. Hardeman, J. G. Hayes, Margaret A. Hayes, J. Hennigan, J. R. Hewett, A. N. Horwitz, M. Howett, J. D. Jackson, R. J. Jameson, A. Jervis, D. D. Johnstone, G. M. Johnstone, Zohra B. Kazi, T. W. Kidd, F. F. Kinnaird, W. A. Kirkpatrick, T. P. Kissack, R. I. Kleinman, Mukulika Konar, Yu Shing Lam, Sheila M. Lane, A. S. Liddell, Ruth Lister, Mary I. Lloyd, Anne E. T. Lodge, W. H. McBay, T. D. McCarthy, Jessie Macdonald, Morag S. Macdonald, J. MacIntosh, M. J. McKenna, A. Mackinnon, J. H. Marks, Helen F. Martin, J. B. H. Martin, P. L. Martin, D. G. May, Prabha Mehra, A. H. Mendoza, B. R. Middleton, N. A. Miles, R. H. D. Miles, A. P. Millar, A. P. Miller, D. D. Moir, Marjorie Monk, J. L. Montagnon, R. D. Morbey, D. F. Morley, J. D. Morris, E. A. Murray, Joan M. Nabarro, Shirley E. Nathan, R. W. A. Nel, P. A. Normandale, R. C. Norton, K. C. Nyman, Irene M. F. Ondatje, Heather M. Panton, E. R. Parry, Mary C. W. Paterson, D. C. Pattison, P. Pau, Barbara M. Philpott, A. C. C. Pinion, G. H. G. Poole, Gertrude M. Pullan, T. A. I. Rees, J. G. Rider, K. J. Roberts, C. Rooney, J. J. O'C. Rorke, A. D. Rose, L. Rose, D. P. Rough, P. C. Roy, F. C. Rutter, P. E. H. Rutter, R. G. Seagar-Thomas, Noel P. Shannon, J. Sharp, Mary E. T. Sheridan, H. A. D. Shirlaw, J. Ll. Skinner, A. I. Smith, D. P. Q. Smith, L. Smith, R. C. Smith, A. G. Stephens, Monnica C. Stewart, A. M. Stobie, G. F. Stone, H. L. Symon, G. W. Taylor, Mary T. Taylor, J. C. Turner, Barbara V. Tyman, Lilian S. Underhill, T. W. West, I. J. Waite, Mary J. Watson, J. N. Wattie, H. B. G. Webb, A. L. Wells, W. G. Wenley, Constance M. Wilkinson, F. C. Wilkinson, R. Williams, E. A. Wilson, Janet W. Worling, Margaret E. Wort, V. Zuck.

ROYAL COLLEGE OF PHYSICIANS OF CANADA

At a recent examination the Fellowship of the College was awarded to W. F. T. Tatlow, M.D., M.R.C.P.

Vital Statistics

Week Ending February 6

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,015, whooping-cough 1,984, diphtheria 19, measles 1,487, dysentery 624, acute poliomyelitis 21, paratyphoid fever 4, and typhoid fever 0.

Infectious Diseases

The largest variations in the trends of infectious diseases in England and Wales during the week ending January 30 were decreases of 117 for whooping-cough, from 2,357 to 2,240, and 80 for scarlet fever, from 1,138 to 1,058, and increases of 84 for measles, from 1,106 to 1,190, and 82 for dysentery, from 490 to 572.

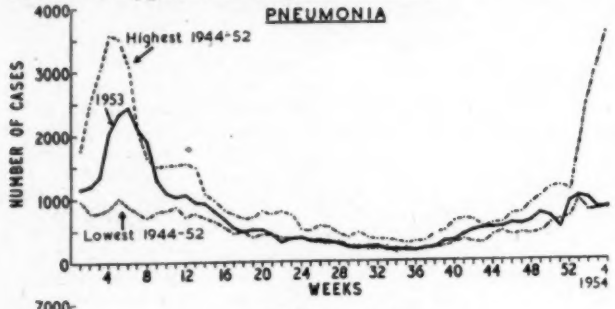
The largest falls in the trends of whooping-cough were 67 in Southampton, from 117 to 50, 38 in Lincolnshire, from 63 to 25, and 34 in Staffordshire, from 113 to 79. Only small variations occurred in the local trends of scarlet fever. The largest variations in the returns for measles were a decrease of 131 in Cumberland, from 196 to 65, and increases of 92 in Staffordshire, from 128 to 220, and 54 in Norfolk, from 166 to 220. The chief centres of infection in the last two counties were Stoke-on-Trent C.B. 148 and Norwich C.B. 104. 16 cases of diphtheria were notified, being 2 fewer than in the preceding week. The chief features of the returns for diphtheria were a decrease in Lancashire from 9 to 1 and a rise in Staffordshire from 1 to 5 (Coseley U.D. 3).

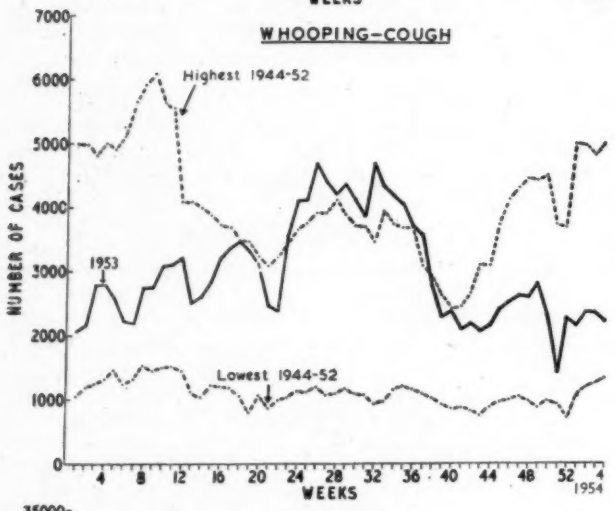
22 cases of acute poliomyelitis were notified. These were 14 fewer for paralytic and 1 fewer for non-paralytic cases than in the preceding week. The only areas with multiple cases were Gloucestershire, Mangotsfield U.D. 3, and Wiltshire, Calne and Chippenham R.D. 2.

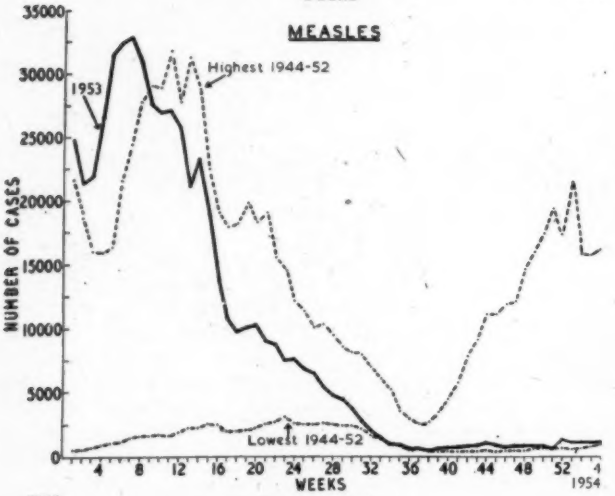
The largest returns for dysentery were London 115 (Islington 40, Finsbury 11), Yorkshire West Riding 113 (Bradford C.B. 47, Leeds C.B. 28), Lancashire 76 (Bolton C.B. 16, Swinton and Pendlebury M.B. 16), Middlesex 53 (Enfield U.D. 14, Willesden M.B. 14), Nottinghamshire 30 (Worksop M.B. 27), Southampton 16 (Christchurch M.B. 10), Norfolk 15 (Norwich C.B. 15), Gloucestershire 15 (Bristol C.B. 15), and Warwickshire 15 (Birmingham C.B. 15).

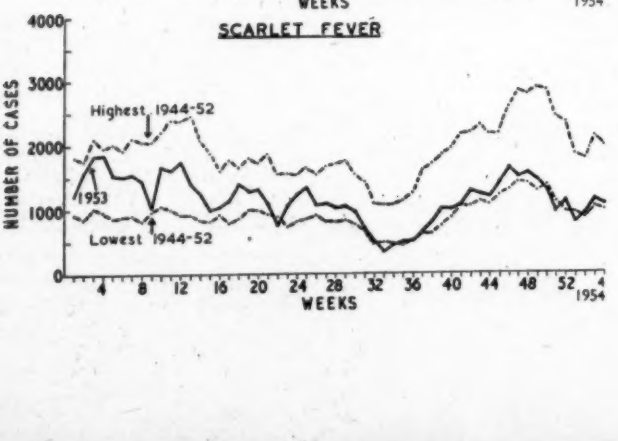
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - - - -, the figures for 1953–4 thus ————. Except for the curves showing notifications in 1953–4, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 30** (No. 4) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	16	1	8	0		24	1	9	1	0
Dysentery	572	115	173	3	6	435	32	110	6	0
Encephalitis, acute	1	0	0	0		8	2	0	0	
Enteric fever:										
Typhoid	1	0	0	1	2	1	0	0	0	7
Paratyphoid	3	0	0	1		7	0	2(B)	0	0
Food-poisoning	97	13		1		60	6		1	
Infective enteritis or diarrhoea under 2 years				13	22				13	12
Measles*	1,190	11	54	27	249	26,460	1470	273	49	178
Meningococcal infection	50	1	20	1		45	5	12	0	2
Ophthalmia neonatorum	32	0	1	1		32	2	5	0	
Pneumonia†	825	48	199	8	19	2,029	183	245	61	25
Poliomyelitis, acute:										
Paralytic	16	2	0	0	2	22	2	1	0	4
Non-paralytic	6	0				7	1			
Puerperal fever§	194	31	12	1		282	32	16	0	
Scarlet fever	1,058	57	192	23	27	1,850	85	292	41	57
Tuberculosis:										
Respiratory	729	91	146	35				165	27	
Non-respiratory	87	1	22	4				21	4	
Whooping-cough	2,240	83	352	47	109	2,799	153	159	35	187

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	1	0	0		0
Dysentery	1	0		0		0	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	1	2	0	1	11	2	3	1	1
Influenza	29	3	0	0	3	313	54	2	2	5
Measles		0	0	0	0		0	1	0	0
Meningococcal infection		0	0				0	1		
Pneumonia	310	51	38	9	8	654	153	29	15	11
Poliomyelitis, acute	1	0			0	4	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	116	19	15	3	7	145	28	20	2	7
Non-respiratory		1	1	1	2		5	3	1	1
Whooping-cough	0	0	1	0	0	4	0	1	0	0
Deaths 0–1 year	227	33	31	12	13	321	37	38	13	14
Deaths (excluding stillbirths)	6,188	852	633	123	179	8,403	1542	621	143	189
LIVE BIRTHS	6,953	1023	926	204	354	7,437	1103	849	228	419
STILLBIRTHS	189	20	31			211	27	27		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Diphtheria Prophylaxis.—The number of babies under 1 year receiving diphtheria immunization in England and Wales is disturbingly low. Instead of the 75% regarded as the desirable immunization target, in 1952 only 31% were immunized and the figure for the first half of 1953 is hardly any better. The Ministry of Health is therefore calling for renewed efforts on the part of all local authorities to improve the rate (Circular 5/54). The figures for diphtheria deaths and notifications during the last 10 years show a remarkable change: in 1944 there were 934 deaths and over 23,000 notifications; in 1953 the provisional figures are 24 deaths and 240 notifications, but, in the words of the Ministry circular, "if parents leave their children unprotected there may be a return of diphtheria outbreaks."

Hunterian Society.—The annual dinner of the Hunterian Society was held on February 11 with the president, Sir Heneage Ogilvie, in the chair. In proposing the toast of the Hunterian Society Sir Alan Herbert said that when he recalled all the stories he had read about medical students he was astonished to see how impressive was this gathering of beautifully dressed and decorated doctors. After a characteristic tribute to John Hunter—"a pioneer in all my favourite things, like the placental circulation"—Sir Alan praised the Society, saying he was pleased to find it was not composed of "ugly little groups discussing diseases of the bladder." In reply Sir Heneage Ogilvie said that John Hunter had established scientific surgery. He paid a special tribute to Mr. Mortimer Wolff for his great efforts in past years in bringing the Society up to its present strength. Mr. R. H. Metcalfe proposed the toast of the Lord Mayor and Corporation of the City of London, and Sir Noel Bowater replied. Sir Allen Daley proposed the toast of the guests and kindred societies, and responses were made by Miss Pat Hornsby-Smith, M.P., and Mr. E. W. Riches.

World Health Organization.—The executive board of W.H.O., under the chairmanship of Dr. Melville Mackenzie, has concluded its preparatory work for the seventh World Health Assembly in May. For 1955 a budget of $10,300,000 is proposed, a 21% rise on this year's sum. The executive board warns the Assembly that any significant cut in the budget would have serious effects on W.H.O.'s programme. During its recent session the board also decided to look into two important public health problems, the chemical adulteration of food and the protection of workers and the general public against irradiation hazards.

World Medical Journal.—The World Medical Association has for the past few years published each quarter the *World Medical Association Bulletin*. This has now been renamed the *World Medical Journal*, and is, as was the *Bulletin*, the official journal of the W.M.A. The *Bulletin* was edited by Dr. Morris Fishbein, who has now been succeeded by Dr. Austin Smith, Editor of the *Journal of the American Medical Association*, and he is assisted by a small editorial committee. Dr. Louis H. Bauer, Secretary-General of the W.M.A., is business manager of the new journal, which now appears with a new look in the shape of a well-designed cover and an attractive lay-out of the text. The *World Medical Journal* is to appear bimonthly instead of quarterly, is published in the three official languages of the W.M.A.—English, French, and Spanish—and contains articles of information that should be of much interest to members of the 46 national medical associations which make up the membership of the W.M.A. The journal is widely circulated throughout the world, and the annual subscription to it for British readers is £1 15s. Anyone wishing to subscribe should write to Dr. Louis H. Bauer, World Medical Association, 345, East 46th Street, New York, 17, N.Y., U.S.A. The January number opens with an article entitled "Relations between the Medical and Non-medical Press," by Mr. John Pringle, public relations officer to the B.M.A. This article is based on a paper read by Mr. Pringle at the Medical Journalism meeting of the W.M.A. at The Hague last September. Other communications include one on "The Medical Aspects of Social Security," by Dr. Gunnar Gundersen, "Conditions for Practising Medicine in Canada," by Dr. L. Gerin-Lajoie, and "On the Retirement of Doctors," by Dr. P. Cibrie, of Paris.

Bicentenary Celebrations at Madras.—At the Government General Hospital, Madras, on December 19 celebrations were held to commemorate the bicentenary of its founding by the East India Company, the golden jubilee of the discovery of the causative organism of kala-azar by Lieutenant-Colonel Charles Donovan, I.M.S., and the opening of the cancer pavilion, which had been given by the Madras Cancer Association. Mr. Sri Prakasa, inaugurating the celebrations, paid tribute to the East India Company, which had done so much in building up institutions such as the hospital in Madras for the good of the community. The residence of the first agent of the Company had been used for housing the hospital. Dr. D. V. S. Reddy, professor of physiology in the Madras Medical College, introduced Sir A. Lakahmanaswami Mudaliar, Vice-Chancellor of Madras University, who unveiled a tablet to commemorate Colonel Donovan's discovery in 1903. Dr. S. Muthulakshmi Reddy opened the cancer pavilion.

Health Information Digest.—The Central Council for Health Education has published the first issue of a new half-yearly journal, *Health Information Digest*. The journal provides summarized information on important health problems. It is intended for those who are unable to search the literature for themselves. The first issue deals with the fluoridation of water supplies, mental deficiency, and the future of the child welfare centre. The journal is edited by Dr. A. J. Dalzell-Ward and Mrs. Priscilla Milton. It may be obtained from the Central Council for Health Education, Tavistock House North, Tavistock Square, London, W.C.1, or from leading booksellers, price 2s. 6d. a copy or 5s. annually, post free.

Journals for Chemists.—Two additions to the literature on chemistry have just made their appearance. *Current Chemical Papers* is a monthly classified world list of new papers in pure chemistry. It is published by the Chemical Society, Burlington House, London, W.1, price £2 10s. per annum (£4 10s. by air mail). *Analytical Abstracts* deals with all branches of analytical chemistry and is published monthly by the Society for Analytical Chemistry, 7–8, Idol Lane, London, E.C.3, price 50s. per annum.

Doctors with New Zealand Himalayan Expedition.—Sir Edmund Hillary's expedition to the Barun Glacier includes two British doctors. Dr. Michael Ball is the expedition's medical officer, and in addition there is Mr. R. C. Evans, F.R.C.S., who reached the south summit of Everest last year.

A Rare Treatise.—John Banester's *Antidotarie Chyrurgicall*, which was recently the subject of a note in the *Journal* (February 6, p. 329), was sold for £400 on February 8.

Mr. Norman Hodgson, lecturer in surgery at Durham University and surgeon to the Royal Victoria Infirmary, Newcastle-upon-Tyne, has been appointed to a University professorship of surgery personal to himself. Professor A. G. R. Lowdon, who last year succeeded Professor F. H. Bentley in the chair of surgery at Durham University, continues as head of the department.

Dr. Donald McI. Johnson, a former member of the Liberal Party's national council, has been adopted by the local Conservative Party Council as Conservative candidate for Carlisle.

Dr. J. N. Loring has been appointed Apothecary to the Queen Mother's Household. Dr. Loring is also Apothecary to the Queen's Household and held the same appointment to the late Queen Mary's Household.

Journal Index.—The half-yearly indexes to Volume II of the *Journal* and the *Supplement* for 1953 are now being sent to members who receive them regularly and to subscribers. Members who have not previously asked for the indexes can obtain copies, post free, on application to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

COMING EVENTS

Irish Medical Association.—The annual meeting will be held at Killarney from July 7 to 10. Opening speakers include Mr. Terence Millin, on "Urological Emergencies in General Practice"; Dr. William O'Donovan, on "Drug Eruptions, Old and New"; and Sir James Spence, on "Recent Advances in Paediatrics." There will also be clinical demonstrations at the Mental Hospital, Killarney. Further information from the medical secretary, 10, Fitzwilliam Place, Dublin.

Third International Congress of Nutrition.—The congress is to be held, under the auspices of the International Union of Nutritional Sciences, in Amsterdam from September 13 to 18. The programme will include sessions on the following topics: "Overnutrition and Disease," "Nutrition and Liver Disease," "Parenteral Nutrition," "Nutrition and Psyche," "Non-nutrient Foreign Chemical Substances in Foods (Intentional and Non-intentional Additives)." Nutrition workers in Britain who would like to participate in the discussions are invited to submit a title and a short synopsis (not exceeding 200 words) to Dr. G. H. Bourne, honorary secretary of the Nutrition Society, London Hospital Medical College, Turner Street, London, E.1, by February 28.

Dr. Paul Wood will deliver the Joseph Strickland Goodall Memorial Lecture at Apothecaries' Hall, Black Friars Lane, Queen Victoria Street, London, E.C.4, on March 24 at 5 p.m. His subject is "An Appreciation of Mitral Valve Disease."

National Association for Mental Health.—The annual conference will be held on March 25 and 26 at Friends House, Euston Road, London, N.W.1. The conference will be opened by Sir Walter Monckton, and the theme will be "Strain and Stress in Modern Living: Special Opportunities and Responsibilities of Public Authorities." Further particulars may be obtained from the conference secretary, National Association for Mental Health, 39, Queen Anne Street, London, W.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, February 22

HUNTERIAN SOCIETY.—At the Mansion House, 8.30 p.m., Hunterian Oration by Sir Gordon Gordon-Taylor: A Famous Hunterian—Sir Charles Bell.

INSTITUTE OF PSYCHIATRY.—5.30 p.m., lecture-demonstration by Dr. E. Stengel.

MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Medical School, Manchester University, 9 p.m., Dr. W. H. Patterson: Convulsions in Infancy and Early Childhood.

Tuesday, February 23

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. R. R. Race, F.R.S.: Blood Groups.

KEATS-SHELLEY MEMORIAL ASSOCIATION.—At Anatomy Theatre, Guy's Hospital, 5 p.m., Mr. F. N. Doubleday: Portraits of John Keats.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Goulstonian Lecture by Dr. A. W. Woodruff: Natural History of Anaemia Associated with Protein Malnutrition.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Mr. Bryan Williams and Mr. J. D. Martin: Deep Transverse Arrest.

WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., Dr. C. Worster-Drought: Blood-vessel Tumours of the Brain. Demonstration illustrated by lantern slides.

Wednesday, February 24

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. Jeannie E. Stirrat: Dynamics and Preventive Mental Health.

EDINBURGH CLINICAL CLUB.—At Alyn Rooms, Edinburgh, annual dance.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Foreign Body Granulomas.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. R. C. Higham: Diminished Fertility in the Male.

●LONDON UNIVERSITY: DEPARTMENT OF EXTRA-MURAL STUDIES and ATOMIC SCIENTISTS' ASSOCIATION.—At Beveridge Hall, Senate House, 7 p.m., Professor Kathleen Lonsdale, F.R.S.: Atomic Energy and Moral Issues.

MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Medical School, Manchester University, 4.30 p.m., Professor R. V. Christie: Dyspnoea.

MEDICAL SOCIETY OF LONDON.—8.30 p.m., Lettsomian Lecture by Mr. Norman C Tanner: Surgery of Peptic Ulcers and its Complications.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., James Watson Lecture by Dr. A. S. Douglas: Modern Concepts of Blood Coagulation and its Disorders.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. D. W. Pearce: lecture-demonstration in psychiatry.

SOCIETY FOR ENDOCRINOLOGY.—At Royal Society of Medicine, 10 a.m., joint meeting with Endocrinological Section of Royal Society of Medicine. Symposium: Technique and Significance of Oestrogen Determinations.

Thursday, February 25

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Lord Stamp: Action of Bacterial Enzymes on Immunizing Antigens.

GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—At Glasgow University Union, 7.30 p.m., B.M.A. Lecture by Dr. D. A. Williams: Problem of Asthma.

●INSTITUTE OF CHILD HEALTH.—5.30 p.m., Dr. D. Stafford-Clark: Prevention of Delinquency.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Pathology of Lupus Erythematosus.

LEEDS UNIVERSITY.—At Littlewood Hall, General Infirmary at Leeds, 4.15 p.m., Professor Dorothy S. Russell: Methods of Growth and Spread in Primary Intracranial Tumours.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Symposium: Mitral Disease. Openers, Dr. G. R. Ellis, Dr. R. J. Keating, and Mr. F. R. Edwards.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Headington, Oxford, 8.30 p.m., Mr. Geoffrey Platt: Recurrent Dislocation of the Elbow and its Treatment; Mr. M. H. M. Harrison: Recurrent Dislocation of the Patella and its Treatment.

OXFORD UNIVERSITY.—At Southfield School, Glanville Road, Cowley Road, Oxford, 8 p.m., Dr. A. G. M. Weddell: Science and Medicine.

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Dr. R. H. Mole: Fission Products.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Goulstonian Lecture by Dr. A. W. Woodruff: Natural History of Anaemia Associated with Protein Malnutrition.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Professor J. M. Yoffey: Bone Marrow.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., neurology demonstration by Dr. D. Williams.

SURREY INTER-HOSPITAL PSYCHIATRIC ASSOCIATION.—At Banstead Hospital, Sutton, 8 p.m., clinical meeting. Papers by Dr. I. F. Collie, Dr. T. Grygier, and Dr. R. Wheeler.

●WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At South Kensington Hotel, 7.30 for 7.45 p.m., dinner meeting. 8.30 p.m., Dr. A. E. Martin: Smog.

Friday, February 26

INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. D. I. Williams: Alopecia.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical meeting for general practitioners. Mr. G. H. Howells: Modern Trends in Treatment of Cancer of the Ear, Nose, and Throat.

LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., discussion to be opened by Dr. M. M. Burrows: Anaesthesia in Obstetrics.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES.—7.30 p.m., Dr. W. V. Macfarlane and Miss Johns (Almoner): Medico-Social Background of Congenital Syphilis. A discussion will follow.

OSLER CLUB OF LONDON.—At 26, Portland Place, W., 7.45 p.m., Sir Philip Manson-Bahr: Life and Work of Sir Patrick Manson. Discussion to be opened by Professor P. C. C. Garnham.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor W. A. Mackey: Splenectomy.

●ROYAL INSTITUTION.—9 p.m., Dr. C. H. Andrewes, F.R.S.: The Common Cold.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Sir V. Zachary Cope: How Medicine Helped to Win the War of 1939-45.

APPOINTMENTS

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—W. A. Heaton-Ward, M.B., Ch.B., D.P.M., Medical Superintendent to Stoke Park Colony Group, Bristol; C. T. Vincent, M.B., B.S., Assistant Clinical Pathologist to North Gloucestershire Clinical Area; Margaret A. Lakeman, M.B., B.S., D.Obst.R.C.O.G., Registrar in Obstetrics and Gynaecology, Camborne-Redruth Miners' and General Hospital, Redruth; Elizabeth P. Champion, M.B., B.S., D.A., Anaesthetic Registrar, Southmead Hospital, Bristol; Kathleen C. Iles, M.B., Ch.B., Registrar in Diseases of the Chest, Bristol Clinical Area; T. C. Gibson, M.B., B.Chir., Medical Registrar, Royal United Hospital and Royal National Hospital for Rheumatic Diseases, Bath; C. E. C. Wells, M.B., B.S., M.R.C.P., Senior Medical Registrar, Bath Clinical Area.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Grant.—On February 7, 1954, at Derby, to Patricia, wife of Dr. P. W. Grant, of Wayside, Duffield, Derby, a son—James Walker.

Meek.—On January 27, 1954, at Bristol Maternity Hospital, to Eileen, wife of Edward S. Meek, M.B., Ch.B., a daughter.

Nicholas.—On January 28, 1954, at Woodmount, Linden Road, Clevedon, Somerset, to Eileen (formerly Moore), M.B., Ch.B., wife of John C. Nicholas, L.D.S., a sister for Jennifer and John—Margaret.

Perry.—On February 7, 1954, at the Cardiff Royal Infirmary, to Dr. M. Elizabeth R. Perry (formerly Thomas), wife of Dr. C. Lynn Perry, a son.

GOLDEN WEDDING

Vartan—Hepworth.—On February 16, 1904, at Augustine Church, Edinburgh, Charles Samuel Vartan, M.B., Ch.B., to Florence Ethel Hepworth. Present address: Flat 4, 10, The Paragon, Blackheath, London, S.E.

DEATHS

Allan.—On January 20, 1954, in hospital, the result of an accident, Alexander William Allan, M.D., of 3, East Heath Road, Hampstead, London, N.W., late of Skegness, Lincs, aged 85.

Angus.—On January 24, 1954, at 6, Church Street, Epsom, Surrey, Dorothy Graham Angus, M.R.C.S., L.R.C.P.

Brady.—On January 22, 1954, in a nursing-home, Dublin, Michael Richard Brady, M.D., of 150, Harley Street, London, W.

Brown.—On January 20, 1954, at 2, Reddings Road, Moseley, Birmingham, James Duncan Brown, M.B., Ch.B., D.M.R., late of Mukden, Manchuria.

Fisher.—On January 20, 1954, at his home, Wells Road, Fakenham, Norfolk, William Henry Fisher, M.B., B.Ch., aged 87.

Steward.—On January 10, 1954, at Elleray Bank, Windermere, Edward Simmons Steward, F.R.C.S., aged 83.

Wrench.—On January 8, 1954, at his home, 5, Victoria Road, Karachi, Pakistan, Guy Theodore Wrench, M.D., formerly of London, W., and Reading, Berks.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Smoking Cures

Q.—*Please tell me what you think about the various smoking cures one hears about. Are they any good?*

A.—"Cures" for smoking, as for other forms of addiction, fall into three classes. In the first are those which aim at making the act of indulgence so unpleasant that it is soon renounced. The most impressive example of this class is the use of "antabuse" (tetraethylthiuram disulphide) in alcoholism. In the case of tobacco, however, no such effective agent exists: most of the methods suggested make the mouth dry or impart an unpleasant taste to tobacco smoke. Stramonium has been used for the first purpose; the second can be accomplished by a mouth wash of 0.25% silver nitrate or 0.01% copper sulphate or by a pill containing ferrous sulphate and alum. The psychotherapeutic approach has not been neglected and it has been recommended that unpleasant associations with the act of smoking should be established by suggestion.

The second method is by gradual withdrawal; this is, of course, familiar in the treatment of narcotic drug addiction. In its simplest form it would consist in gradual reduction in the number of cigarettes smoked, advice often tendered but seldom followed. In its more radical form smoking is forbidden and nicotine administered in gradually reducing doses, either by subcutaneous injection or in the form of pastilles. This method makes the assumption that the desire to smoke and nicotine addiction can be equated. Although addiction is certainly of importance, the causes of the habit are undoubtedly more complex. Smoking has become something of a social observance and the act has acquired a ritualistic significance.

The third class of "cures" attempt to abolish the desire to smoke. Their shortcomings are due to our ignorance of the origins of this desire. It has been claimed that the administration of lobeline sulphate by mouth reduces the desire to smoke. Lobeline is derived from a plant the leaves of which have long been smoked by some Indian tribes, and its pharmacological effects are similar to those of nicotine. The recommended dose of 8 mg. may cause a metallic taste, heartburn, epigastric pain, fainting, vomiting, salivation, lethargy, inability to concentrate, and fullness of the head. These symptoms may last for as long as four hours, and it will occasion no surprise that the subject experiences no desire to smoke while they endure. Other attempts to abolish the desire to smoke include hypnosis, simple exhortation, and admonition aimed at implanting in the smoker's mind notions of guilt, uncleanliness, and pusillanimity.

It is difficult to assess the efficacy of these various cures. Patients seldom ask the doctor's advice on how to give up smoking; *per contra*, doctors frequently issue a bland injunction to abstain from tobacco without suggesting any means by which the renunciation can be made easier. It is a matter of common observation that a heavy smoker can stop smoking at no greater cost than a few days' shortness of temper. Determination is the only quality required; but it seems probable that one who lacks sufficient to give up smoking without a cure will certainly not possess enough to persevere with the various cures recommended. The very desire for a smoking "cure" shows that the smoker is not prepared to take full responsibility for his addiction and is anxious to be able to attribute his failure to abstain from it to the inefficacy of the cure rather than to the weakness of his will.

The Serum-sensitive Recruit

Q.—*A boy, aged 13, was discovered to be serum sensitive about five years ago. An injection of A.T.S. (1 minim—0.6 ml.—intradermally) produced a violent local reaction and a temperature of 103° F. (39.4° C.). He has never had any serum injections since. The boy wants to join the Navy. Would it be safe to give him T.A.B. injections? If not, can he be desensitized to horse serum generally?*

A.—The degree of sensitivity of this boy to various allergens might be investigated in the first instance, partly by cross-examination about his history, including reactions to previous inoculations of all types, and partly by attempting active immunization against diphtheria and tetanus if this has not been done already. The reaction to the Schick control injection might also give useful information. Most subjects who are allergic to serum can be immunized actively with diphtheria or tetanus toxoid without much trouble from reactions. (Diphtheria prophylactic T.A.F. should be avoided as it contains a small amount of serum.) Active immunization is indicated where possible, because it should obviate the emergency use of diphtheria or tetanus antitoxic serum.

It should not be assumed that this youth is very sensitive to horse serum on the basis of what happened five years ago after an intradermal injection. If he should require serum again, a small "trial dose" given subcutaneously is much the best procedure.[1]

With regard to T.A.B. injections, it is altogether exceptional for reactions to be so severe that immunization has to be discontinued. With this possibility in mind, however, it would obviously be wise to make a preliminary sensitivity test using a 1:100 dilution of vaccine subcutaneously. There is no horse serum in T.A.B. vaccine, the reactions to which are unrelated to sensitivity to serum. In any case it is probably impossible to desensitize a patient to horse serum.

REFERENCE

[1] Laurent, L. J. M., and Parish, H. J. (1952). *British Medical Journal*, 1, 1294.

Pharaoh's Ants

Q.—*My small hospital has had a plague of minute ants, reddish in colour and about 3 mm. long, called Pharaoh's ants by the pest officer. They are found in kitchens, dining rooms, passages, and in the patients' beds, and have resisted all attempts at eradication. Is there a cure? The state of mind of a patient in a plaster jacket with numbers of ants crawling about in his bed is becoming maniacal.*

A.—Pharaoh's ant (*Monomorium pharaonis* L.) is a fairly common and very troublesome pest of hospitals and other large steam-heated buildings. Although it has been with us for over 100 years it does not live out of doors in Britain, but forms nests in crevices inside the walls and floors of buildings. It probably travels from one site to another in packing cases and similar goods.

The most effective treatment seems to be spraying with chlordane dissolved in kerosene. The trails of ants should be traced back to the nest or nests (there may be more than one). Then the walls and ceilings in the neighbourhood should be thoroughly sprayed. It may be advisable to employ a reliable pest control firm for this purpose. One good treatment may effect a cure, but a watch should be maintained for survivors.

As a temporary measure to protect the beds of individual patients, the legs should be stood in tins containing oil or strong carbolic acid.

Phenylbutazone and Pulmonary Tuberculosis

Q.—*Is phenylbutazone contraindicated in the presence of pulmonary tuberculosis?*

A.—There is no special reason why phenylbutazone should not be given in the presence of pulmonary tuberculosis except that it occasionally has unpleasant and dangerous side-effects such as agranulocytosis, peptic ulceration, exfoliative dermatitis, and salt retention.

Acid-forming Foods

Q.—*Which articles of food are acid forming and which alkali forming? Many patients complain of "acidity" and seek advice about diet, and we doctors give them conflicting advice. Some patients are told, for example, that oranges and grapefruit are acid forming and they avoid them permanently. But are not the organic acids such fruits contain broken down in the body to carbonates and therefore alkali forming?*

A.—The acidogenic value of a food is expressed as the volume of 0.1 N acid which would be produced if all the phosphorus, sulphur, and chloride in the food were fully oxidized to phosphoric, sulphuric, and hydrochloric acid respectively. The alkalogenic value of a food is expressed as the volume of 0.1 N alkali which would be produced if all the sodium, potassium, calcium, and magnesium in the food were converted into their respective hydroxides. Tables of these values are readily available (e.g., *Medical Research Council Special Report Series No. 235*, "The Chemical Composition of Foods," by R. A. McCance and E. M. Widdowson), where the excess of acidogenic or alkalogenic components in a large variety of foods is given. As examples, predominantly acidogenic foods are eggs, lean meat, fish, and cereals, whilst potatoes, vegetables, fruit, and leguminous foods are predominantly alkalogenic.

It will be seen from the above that the organic acids contribute neither to the acidogenic nor to the alkalogenic value of a diet, and do not appreciably alter the acid-base equilibrium of the body when taken in food, because they are completely oxidized to carbon dioxide and water, which are rapidly eliminated. If, however, these acids are present as their salts, the metals so combined would contribute to the alkalogenic value of the diet.

Selection for Work in Compression Chambers

Q.—*In examining men for fitness for working in compression chambers, are there any special points to bear in mind?*

A.—The routine examination should be very thorough, especially of the heart and lungs. It is also advisable to test the locomotor system and ask about previous injury, especially fractures, as such people are prone to "bends" at the site of the injuries. If enough candidates are available, then any history of serious lung disease (pneumothorax, complicated pneumonia, minimal tuberculosis) should mean exclusion, even though the present condition is satisfactory. It is now considered that, with even a minor lung lesion, breathing from a closed apparatus during severe pressure changes may cause serious accidents, such as pneumothorax and perhaps even aero-embolism. If no breathing apparatus is used under pressure this risk is not present. Men with even mild bronchitis or bronchospasm should also be excluded. For all these reasons a routine *x*-ray picture of the lungs is highly desirable.

Any nose or throat abnormality or disease, unless easily remediable, should also mean exclusion. The ears should be examined carefully and patency of the eustachian tubes checked by "ear clicking." Middle-ear disease of any degree contraindicates exposure to pressures. All selected candidates should be tested for easy pressure equalization in the middle ear by actual compression in a chamber. Those who can clear their ears but with some difficulty will finally suffer ear damage due to repeated congestion and oedema of the middle ear over long periods and are therefore best excluded.

Surprisingly enough, men with claustrophobia may volunteer for this work, and all candidates should be watched carefully during the compression tests. The behaviour of each man when breathing in a closed circuit is also a useful indication of suitability for this type of work. Finally, if possible, men of stable and moderate temperament should be selected.

Hypertension and Nocturnal Frequency

Q.—*Is active treatment (for instance with hypotensive drugs) indicated in a middle-aged man with essential hypertension (B.P. 260/130) whose only symptom is nocturnal frequency of micturition (3–5 times)? Fluid restriction, barbiturates, and belladonna have failed to relieve the nocturnal frequency.*

A.—Although this degree of hypertension suggests a serious prognosis in a male patient I do not think this is simply a problem of high blood pressure. There is no reason why hypertension should cause nocturnal frequency of micturition unless it is complicated by either renal failure or an enlarged prostate (or, of course, some other independent cause of nocturnal frequency). I do not think one can discuss treatment without an investigation of renal function and prostatic condition. There is no reason to expect that treatment directed solely to the hypertension will cure the frequency.

Ferrous Gluconate

Q.—*Has ferrous gluconate any advantages over other iron preparations in the treatment of an iron-deficiency anaemia?*

A.—Ferrous sulphate in tablet form in a dose of 3 to 5 gr. (0.2 to 0.32 g.) three times a day is a cheap and effective form of iron therapy, and it is seldom that any other preparation need be employed. Nevertheless ferrous sulphate is a gastric irritant, and in really big doses always gives rise to vomiting. A very few patients are peculiarly susceptible to its nauseating effect, and in them even ordinary doses may produce vomiting. There seems little doubt that ferrous gluconate does not have this disadvantage, and it is a perfectly effective form of iron therapy.

Ocular Side-effects of Streptomycin

Q.—*Does streptomycin give rise to any subjective ocular symptoms? For instance, does it make patients with refractive errors more liable to complain of their eyes?*

A.—Streptomycin is not known to give rise to any subjective ocular symptoms, nor does it aggravate existing symptoms. Some years ago, when the drug was not available in as pure a form as it is to-day, serious toxic effects, including optic atrophy, were reputed to occur. Such complications are no longer to be feared.

Are Cases of Disseminated Sclerosis Spared Other Diseases?

Q.—*Does disseminated sclerosis show a negative correlation with any other diseases, e.g., diabetes?*

A.—There is no recognized negative correlation between disseminated sclerosis and other diseases.

"Any Questions?" Book.—The second book of selected "Any Questions?" is available, price 7s. 6d. (postage 6d.). Copies may be obtained either direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers.

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